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exploring the use of a NI TI stent and MRI delineation

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– EXPLORING THE USE OF MRI DELINEATION AND A NI-TI STENT AS FIDUCIAL MARKER

BY
LOTTE SANDER

DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
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ENGLISH SUMMARY

A significant increase in the prostate cancer (PCa) incidence has made PCa a major health problem in recent years. Because of the often but unfortunately not always indolent nature of the disease, over-diagnosis and over-treatment are relevant clinical and ethical dilemmas.

External beam radiotherapy (EBRT) is a well established treatment modality for PCa. Accuracy and precision are key words with regard to optimal survival and minimal toxicity and are fundamentals in modern radiotherapy (RT).

Modern imaging has improved the ability to define RT target volumes. Especially treatment margins have been reduced through the use of more accurate treatment planning and image-guided technology.

Increasing doses have lead to increased disease control. Aiming for minimal toxicity after radiotherapy, magnetic resonance imaging (MRI) delineation could be a possible tool, knowing that clinical target volumes (CTV) are up to 30% smaller after on MRI delineation compared to computer tomography (CT) delineation.

The overall aim of the thesis was to explore the use of MRI target planning and a Nicle-Titanium prostate stent as fiducial marker for both MR-CT co-registration and image guided radiotherapy (IGRT).

Paper 1 evaluated toxicity 3 years after high-dose IGRT comparing target planning delineation on MRI and a prostate stent as fiducial with CT target planning and the use of gold markers as fiducials. The treatments were performed with the same radiation dose and planning target volume margins. A significantly smaller CTV was found in the MR-group. The CTV was correlated to a reduction in overall rectal toxicity, but not to a reduction in overall urinary toxicity. In general toxicity symptoms were few and mild. Significantly lower urinary frequency and urinary retention toxicity scores were observed following MRI delineation.

Paper 2 looked into potential risk factors for rectal bleeding after RT. Different clinical and dosimetric factors were analyzed by univariate and multivariate logistic regression analyzes. The overall conclusion was that the CTV was the only robust risk factor augmenting the risk of rectal bleeding after RT.

Five year survival and morbidity data was evaluated in paper 3, of the first patient cohort that underwent EBRT using MRI delineation and the prostate stent as fiducial. Overall survival, cancer specific survival and biochemical progression free survival were in accordance with recently published data. Late urinary and gastro-intestinal toxicity scores ≥grade 2 were also in

accordance with the lowest toxicity rates reported in recent literature using modern RT like IM-RT.

Five year toxicity and quality of life (QoL) data were investigated in paper 4 in two groups of patients using MRI or CT target delineation before PCa RT. The treatments were performed with the same radiation dose and planning target volume margins. Potential correlations with clinical and dosimetric parameters were also investigated.

The mean CTV was 18% larger in the CT group compared to the MR group. Five year toxicities were in general few and mild; no grade 3 or 4 toxicity was found. No difference in overall urinary or rectal toxicity was found. No difference in global health was seen either. The QoL bowel score were significantly lower in the MR group.

The mean rectal dose and high rectal dose volumes were significantly smaller in the MR group. Rectal high dose was correlated to QoL bowel score and overall rectal toxicity.

DANSK RESUME

En betydelig stigning i incidencen af prostata cancer tilfælde har gennem de seneste år sat fokus på prostata cancer behandlingen i Danmark. Prostata cancer er ofte, men langtfra altid en cancer sygdom med et fredeligt sygeforløb. Dette medfølger at overdiagnostisering og overbehandling bliver relevante kliniske og etiske problemstillinger.

Ekstern strålebehandling (RT) er en gennemprøvet og effektiv behandling for prostata cancer. Præcision i forbindelse med strålebehandlingen er afgørende for bedst mulig overlevelse og minimale bivirkninger. Moderne scanningsteknikker har forbedret mulighederne for at definere og afgrænse målet (CTV) for stråleterapien. Øget stråledosis medfører bedre sygdomskontrol.

Indtegning af prostata på MR scanning i stedet for på CT scanning kan være et skridt på vejen mod færre bivirkninger. Det er beskrevet i litteraturen, at indtegnede mål er op til 30 % mindre efter MR indtegning i forhold til CT indtegning.

Målet med denne afhandling var overordnet at evaluere brugen af MR indtegning og en nikkel-titatium prostata stent som markør i forbindelse med MR-CT co-registrering ved billedvejledt strålebehandling (IGRT).

Artikel 1 evaluerede bivirkninger 3 år efter højdosis IGRT og sammenlignede resultaterne efter prostata indtegning på MR og brugen af prostata stenten som markør sammen med indtegning på CT og brugen af standard guld markører. Patienterne blev behandlet med samme stråledosis og strålemarginer. CTV i MR gruppen var signifikant mindre end i CT gruppen. Der blev fundet en sammenhæng mellem CTV og reduktion af rektal toksicitet, men ingen korrelation til toksicitet fra urinvejene. Generelt var bivirkningerne få og milde. Der blev fundet mindre hyppig vandladning og urin retention i MR gruppen.

Artikel 2 undersøgte potentielle risiko faktorer for rektal blødning efter strålebehandlingen. Forskellige kliniske og dosimetriske faktorer blev analyseret ved univariate og multivariate logistiske regressions analyser. Konklusionen blev samlet, at CTV var den eneste robuste risikofaktor for rektal blødning.

Fem års evaluering af den første gruppe patienter der fik IGRT efter prostata indtegning på MR og med brug af prostata stenten som markør blev opgjort i artikel 3. Overlevelsen, den cancer specifikke overlevelse, biokemisk recidivfrihed og bivirkningerne var på niveau med nyeste publicerede data for moderne stråleterapi som f.eks. intensitets moduleret RT (IMRT).

I artikel 4 blev bivirkninger og livskvalitet 5 år efter strålebehandling for de 2 grupper patienter, efter henholdsvis MR indtegning og CT indtegning, opgjort og sammenlignet. Mulige sammenhænge mellem kliniske og dosimetriske parametre blev også undersøgt. CTV var i gennemsnit 18 % større i CT gruppen i forhold til MR gruppen
Generelt var bivirkningerne få og milde. Der var ingen forskel i urogenitale og gastrointestinale bivirkninger. Ingen forskel i livskvalitet overordnet. Den tarm-relaterede livskvalitet var signifikant bedre i MR gruppen. Der var signifikant mindre mean og høj stråledosis til rektum i MR gruppen. Høj dosis (v72Gy) var korreleret til den tarmrelaterede livskvalitet og til de samlede rektale bivirkninger.

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ABBREVIATIONS

3D-CRT: 3-dimensional conformal radiotherapy
IG: image guided
BPFS: biochemical progression free survival
BT: brachytherapy
ADL: activity of daily living
BPFS: biochemical progression free survival
CSS: cancer specific survival
CT: computed tomography
CTV: clinical target volume
CTC-AE: common terminology criteria for adverse events
Dmax: maximal dose in Gy to an organ or tumour target during RT
Dmean: mean dose in Gy to an organ or tumour target during RT
D2cc: minimal dose given to an area of $2cm^3$ of an organ or tumour target receiving the highest dose during RT
EAU: European Association of Urology
EBRT: external beam radiotherapy
ED.: erectile dysfunction
EORTC: European organisation for research and treatment of cancer
GI: gastro-intestinal
GTV: gross tumour volume
Gy: gray
HDR: high dose rate
IGRT: image guided radiotherapy
IMRT: intensity modulated radiotherapy
Interm.: intermediate
IPSS: international prostate symptom score
LDR: low dose rate
LRP: laparoscopic radical prostatectomy
MR: magnetic resonance
MRI: magnetic resonance imaging
OS: overall survival
PCa: prostate cancer
PTV: planning target volume
PSA: prostate specific antigen
RRP: retropubic radical prostatectomy
RTOG: radiation therapy oncology group
RT: radiotherapy
QoL: quality of life
Vx: volume reciving minimum x Gy during RT

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CHAPTER 1. INTRODUCTION

Prostate Cancer (PCa) is today the most common malignant disease in men in Europe (excluding skin cancer). PCa is mainly diagnosed in men above the age of 50. PCa is a major health concern, particularly in the developed countries, because of their greater proportion of elderly men in the population. There has been a significant increase in the PCa incidence over recent years; this has mainly been attributed to the widespread use of prostate specific antigen (PSA) testing (1;2) and an increased consciousness about PCa in the developed countries in general. Since the PSA era PCa patients are now diagnosed without symptoms. This has also lead to a larger proportion of localized cancers among the newly diagnosed patients and consequently a larger proportion of these patients are potential candidates for curative treatments. However, a large proportion of the newly diagnosed PCa will turn out to be indolent tumours. PCa is known as a slowly growing cancer (most cancers develop over 10-20 years), it is a cancer that mainly affects older men, of which many will die of other causes and furthermore the PCa patients often have no symptoms from their cancer disease. Over-diagnosis and over-treatment are therefore relevant clinical and ethic dilemma (3;4). Over-treatment is, in this case, defined as treatment of a disease that causes no threat to the man's well-being during his lifetime (5). Today standard curative treatment for PCa involves surgery, brachytherapy and external beam radiotherapy (EBRT). Observational studies show that different treatment options all offer high rates of tumour control and nearly equal survival rates (6). However, these treatments can all be followed by a substantial number of side-effects. Consequently, both toxicity and Quality of Life (QoL) after treatment should be a major consideration in treatment decision making (7).

With regard to radiotherapy (RT), modern imaging has improved the ability to define radiotherapy target volumes. Especially treatment margins have been reduced through the use of treatment planning and image-guided technology. Increasing doses have lead to increased disease control. Concurrently, technological advances may improve treatment related toxicity and potentially allow for further dose escalation (8).

The purpose of this Ph.D was to explore a new treatment modality using magnetic resonance (MR) imaging target planning and a Nicle-Titanium (Ni-Ti) prostate stent as fiducial marker for both MR-CT co-registration and image guided radiotherapy (IGRT) focusing on the clinical outcome after radical prostate cancer radiotherapy.

CHAPTER 2. PROSTATE CANCER

2.1. EPIDIMIOLOGY

The incidence of prostate cancer increases with age, most frequently diagnosed in men above the age of 50. Over the past 10 years the PCa incidence almost doubled in Denmark; the incidence was 2288 in 2002 and 4316 in 2012 (9). This increase has been explained by the widespread use of PSA as screening tool and an increased public awareness concerning PCa. The Danish PCa mortality rate though, is unchanged during the same period; 1149 in 2002 and 1187 in 2012. This is obviously followed by a dramatic increase in the prevalence; from 8.244 in 2002 to 28.944 in 2012 (9).

2.2. ETIOLOGY

Only few risk factors for the development of clinical PCa have been identified. These include increasing age, ethnic origin and heredity. The frequency of autopsy-detected cancers seems to be almost the same in different parts of the world (10), this is to be seen in contrast to the incidence of clinical PCa that differs significantly between different areas; the incidence being high in Northern Europe and the USA. Interestingly, it has been shown that if Japanese men move from Japan to Hawaii, their risk of PCa increases, and it increases even further if they move to California, approaching the one of American men (11). These findings indicate that exogenous factors affect the risk of progression from latent PCa to clinical PCa. Infections/inflammatory, hormonal, dietary and lifestyle factors are thought to play a role in the development of PCa but no final recommendations have been made yet (12).

2.3. DIAGNOSIS

The opportunistic use of prostate specific antigen (PSA) has brought many asymptomatic patients to a urological service without symptoms. Possible presenting symptoms of PCa include lower urinary tract symptoms (e.g. urgency, frequency, nocturia, weak stream, incomplete bladder emptying and straining) and symptoms attributable to the local extension of the tumour (e.g. haematuria, pain, incontinence, loin pain due to ureteric

obstruction and impotence). In the relatively rare case of patients debuting with metastatic disease, symptoms like bone pain, anaemia and weight loss can be present. The diagnostic approach includes digital rectal examination (DRE), serum concentration of PSA and transrectal ultrasonography (TRUS). The definitive diagnosis is based on the histo-pathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens.

2.4. CLASSIFICATION AND CLINICAL STAGING

The clinical staging of PCa is based on assessment of the primary tumour. PCa is staged as the biopsy-detectable but non-palpable localized tumour (T1), the tumour palpable at digital rectal examination (T2), the tumour with local spread e.g. dissemination through extra capsular extension and seminal vesicle invasion (T3) and the tumour that invades adjacent structures other than the seminal vesicles (T4).
The current standard grading of adenocarcinomas of the prostate is the Gleason score (13). The Gleason score is the sum of the two most common patterns found on core biopsies or operative specimens. Since January 2009 the worst grade has been incorporated in the Gleason score in needle biopsies even if comprising less than 5% of the cancer. Gleason scores considered as PCa range between 6 and 10, with 10 being the most aggressive. The natural history of the development of prostate cancer has been the subject in observational studies with patients with localized PCa. These studies show that the progression from localized cancer to PCa-specific death may take more than 20 years, but obviously depends on clinical stage and Gleason score at diagnosis (14). Recognized prognostic factors are pre-treatment PSA, Gleason grading, number of biopsies with cancer and T-stage (15;16). Prostate cancer patients are classified into 3 groups according to the D'Amico classification:

Low risk:	**Intermediate risk:**	**High risk:**
PSA<10ng/mL **and** clinical stage T1c-T2a and Gleason score <7	PSA≥10 ng/mL, **but** <20ng/mL **or** clinical stage T2b-T2c **or** Gleason score =7.	PSA ≥20 ng/mL **or** clinical stage >T2c **or** Gleason score >7.

CHAPTER 3. TREATMENTS OF LOCALIZED OR LOCALLY ADVANCED PROSTATE CANCER

Albeit, the evidence from observational studies that many localized PCa tumours are biologically indolent, radical treatment of PCa is increasingly popular. This is despite the fact that mortality has not changed the past 10 years and the lifetime risk of death from PCa is only 3% (17). Currently, clinical stage T1c represents 40-50% of new PCa cases (18). Data suggest that many men with localized PCa will not benefit from definitive treatment and that up to 45% of men with PSA detected PCa are candidates for conservative management; the "active surveillance" (19;20). Furthermore, if co-morbidities and a limited life expectance are present, treatment of more localized PCa may be deferred to avoid loss of QoL from the treatment. To some degree overtreatment of this patient group has probably been ongoing in Denmark for years. Patients with localized disease can today be treated with curative intent with surgery, radiotherapy or brachytherapy as the three recognized non-experimental treatments. To date there is no convincing evidence demonstrating survival superiority of any of these approaches to curative treatment for low and intermediate risk patients (21-24). Regardless, all treatments for localized PCa can cause bothersome complications, including urinary, sexual, and bowel dysfunction (6). Determining the need for treatment can be a complex decision and informed patients should make decisions after weighing the benefits and harms of the treatments. Further comparisons are warranted as techniques evolve across all therapies to continue to investigate any potential difference in outcome. High risk patients hold the greatest challenge and selection of therapy for these patients remains controversial (8).

3.1. ACTIVE SURVEILLANCE (DEFERRED TREATMENT)

Acknowledging the dilemma of being diagnosed with a cancer but not knowing if treatment is necessary and possibly being the subject to disabling side effects, deferred treatment – the "active surveillance" is being given more and more attention. Active surveillance aims at finding the proper timing of the intended curative treatment and thereby reducing overtreatment, rather than the delayed application of palliative treatment

options (18;19). Instead of treating the patient immediately after diagnosis, he remains under close surveillance using repeated DRE, PSA monitoring and repeated prostate biopsies. Today only data from non-mature randomized studies with follow-up of less than 10 years are available (24). Active surveillance is therefore only proposed to highly selected low-risk patients.

3.2. SURGERY

The most common radical treatment offered today is radical prostatectomy (RP). This involves removal of the entire prostate gland and resection of the seminal vesicles. With regard to intermediate and high-risk tumours the procedure is accompanied by bilateral pelvis lymph node dissection (24) In recent years robot-assisted laparoscopic prostatectomy is replacing the radical retropubic prostatectomy as golden standard in many centres particularly in Europe and the USA.
The PIVOT study did not show a difference in survival at 10 years between watchful waiting and radical prostatectomy for PSA screen detected men with PSA of < 10ng/ml. There are two randomized clinical trials with long-term follow-up that compared surgery to watchful waiting. These studies effectively reported conflicting results (25;26). The mortality of modern surgery is low (0,5%) (27), but incontinence and erectile dysfunction are common problems (28;29). Selected outcome data are presented in table I.

Table I. Radical prostatectomy outcome data.

Group	Year	Follow-up	Treatment	Risk group	BPFS (%)	OS (%)	CSS (%)
Vassil (30)	2010	5 year	RRP	Interm.	60.2	-	-
Bill-Axelson (26)	2005	10 year	-	-	73	90.4	-
Røder (31)	2011	5 year	RRP	all	71.7	-	-
Merino (32)	2013	5 year	RRP/LRP	all	-	96.2	-

Mitsuzuka (33)	2013	5 year	RRP	<70/≥70year	80.9/77.4	99.5/95.8	99.8/99.5

3.3. BRACHYTHERAPY

Brachytherapy (BT) is also known as internal radiation. It is based on the precise implantation of short-range radioactive seeds directly in the prostate to deliver radiation in the area requiring treatment. The irradiation only affects a localized area around the radiation source and exposure to radiation of healthy tissue farther away from the source is therefore reduced. The treatment is independent of positional changes since the radiation sources retain their correct position in relation to the tumour.

Brachytherapy can be done as mono-therapy – either low-dose-rate (LDR) or high-dose-rate (HDR) – or in combination with EBRT (EBRT in 40-50Gy dose combined with BT boost with either LDR or HDR) (34-36). LDR mono-therapy is carried out with permanent seed implantation in the prostate. Iodine-125 or Palladium-103 is the radioactive element of reference. The standard doses delivered are median 145 Gy for Iodine-125 and median 125 Gy for Palladium-103(35;36).

HDR brachytherapy as mono-therapy is a more recent treatment modality and seems to be associated with high biochemical control rates and low acute toxicity. Temporary needle catheters are placed in the prostate during the treatment, where high radiation dose is delivered over a short period. The radioactive source is usually iridium 192 or cobalt 60. Doses used in a limited number of studies published today are 26-38 Gy in 2-4 fractions (37-42). Long-term follow-up data are not yet available and this treatment is not yet recommended outside formal studies (34).

Combining BT and EBRT, the optimal dose of supplemental external EBRT is so far unclear (24). Likewise, no consensus concerning the optimal timing of each modality has been decided. BT can be given before EBRT, between EBRT fractions, or after completion of EBRT. One randomised trail comparing EBRT alone with EBRT combined with HDR brachy showed a significant improvement in BPFS after the combined treatment compared to EBRT alone (34). There is no benefit from adding neoadjuvant or adjuvant ADT to brachytherapy. A significant correlation has been found between the implanted dose and recurrence rate (43). Selected outcome data are presented in table II and III.

Table II. LDR brachytherapy outcome data.

Group	Year	Follow-up	Treatment	Risk group	BPFS (%)	OS (%)	CSS (%)
Hinnen (44)	2010	5 year	I.125 perm	-	-	-	79
Jabbari (45)	2012	5 year	I-125 perm	-	-	-	93
Morris (46)	2009	5 year	I-125 perm	low-interm	95.6	95.2	99.8
Vassil (30)	2010	5 year	I-125 perm	interm	-	-	89.5
Zelefsky (47)	2007	5 year	I-125 perm	low/interm	96/89	-	-

Table III. HDR brachytherapy outcome data.

Group	Year	Follow-up	Treatment	Risk group	BPFS (%)	OS (%)	CSS (%)
Barkati (48)	2012	5 year	10-11.5 Gy ×3	low-interm	85.1	-	-
Demanes (37)	2011	8 year	7Gy ×6	low-interm	97	95	99
Rogers (40)	2012	5 year	6.5Gy ×6	interm	94	98	100

3.4. RADIOTHERAPY

Radiotherapy has developed into the most important non-surgical treatment modality for cancer. It is a huge research area involving technology, biology

and physics. Definition, visualization and prediction of the target position are crucial components in any radiotherapy treatment. The development of CT, MR and cone-beam CT has made new technologies like conformal RT, intensity-modulated RT and image-guided RT possible.

3.5. TARGET DEFINITION AND DOSE PRESCRIPTION

The clinical target volume (CTV) is defined by the gross tumour volume (GTV) and the area of risk of microscopic spread. A margin is added to construct the planning target volume (PTV) to compensate for the predicted uncertainties in daily patient positioning, tumour movements and regions at high risk of extra prostatic extension (8;49).

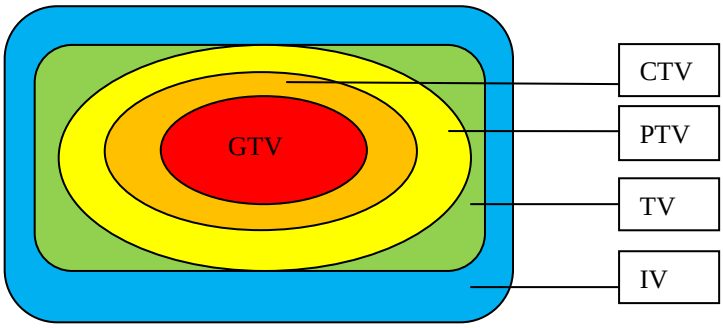

Figure 1. Diagram to illustrate the main radiotherapy volumes. From the ICRU report 50.
GTV: Gross tumour volume (detectable tumour volume).
CTV: Clinical target volume (GTV plus volumes with expected subclinical spread).
PTV: Planning target volume (CTV plus safety margin for movements and deformation, technical uncertainties).
TV: Treatment volume (receiving the prescribed dose).
IV: Irradiated volume (exposed to significant doses with regard to normal tissue tolerance).

In the matter of PCa the CTV is defined as the prostate gland. In the case of seminal vesicle invasion or risk of invasion (Partin tables) (50), the CTV is defined as the prostate gland plus the proximal third part of the seminal vesicles. Normally a margin of 5-15mm is added around the CTV to create the PTV (51;52), as illustrated in figure 2.

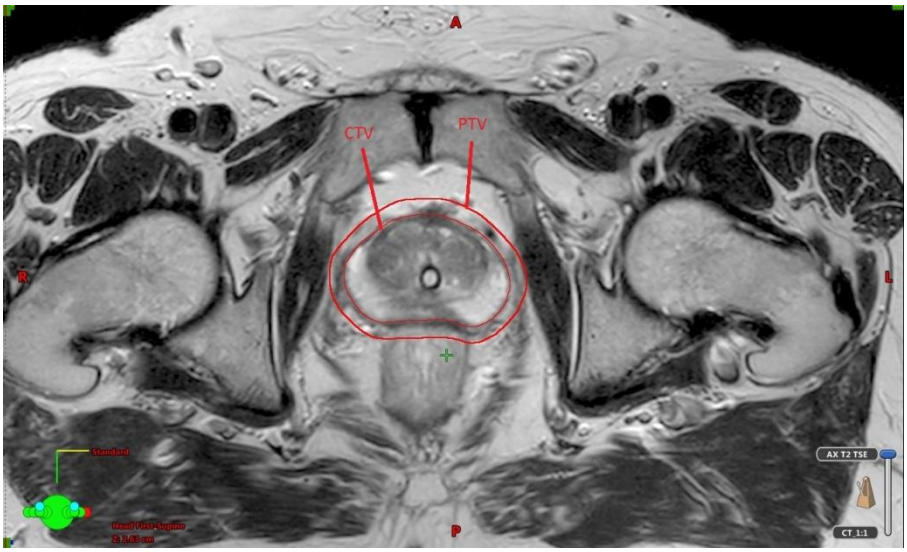

Figure 2: MR slide of a prostate cancer patient. The PTV is generated from the CTV by a uniform expansion of 5 mm in all directions.

Modern imaging has improved the ability to define radiotherapy target volumes. Computed tomography (CT) scans have been used as standard care in most centres for prostate definition, CTV delineation and RT treatment planning. However, limitations of CT include the inability to discriminate regions of disease within the prostate and challenges in differentiating prostate from surrounding fascia and musculature, especially at the apex. Thus, CT target delineation has been demonstrated to lead to an overestimation of the prostate volume Studies have described volume estimations up to 30% larger on CT compared to target delineation on magnetic resonance imaging (MRI) e.g. the good soft-tissue visualization in magnetic resonance (53-55). CT-MR image fusion-based treatment planning allows more accurate prediction of the target volume (8;56). The CT-MR co-registration can be done in several ways; on bony landmarks, with endorectal coil or by intraprostatic fiducial markers. Additional precision may also be gained from fusion of other imaging technologies like ultrasound, magnetic resonance-spectroscopy and novel nuclear medicine images to standard CT (8).

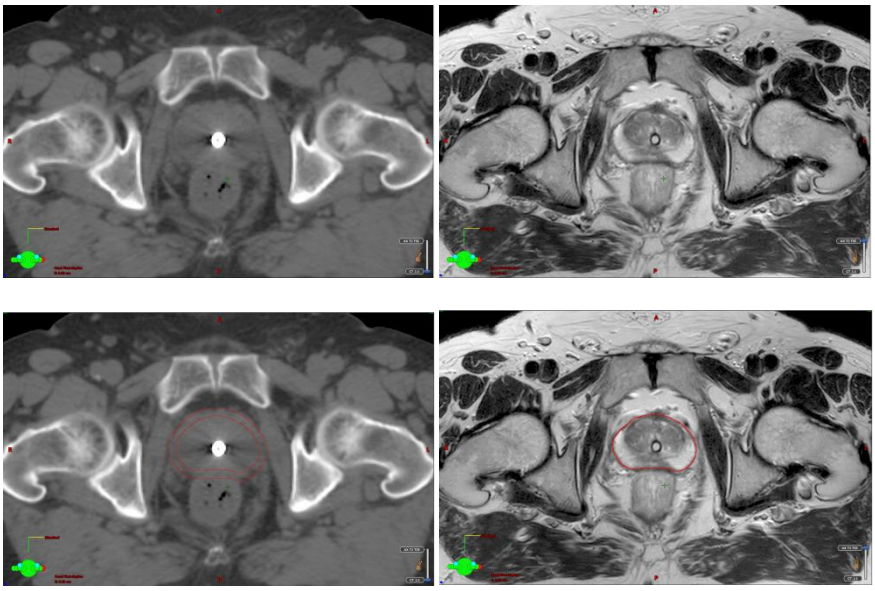

Figure 3. Superior soft tissue differentiation is seen on MRI compared to CT. Left pictures: Prostate delineation on CT. Right pictures: Prostate delineation on MRI.

3.6. DOSES AND FRACTIONS

Different dose and fraction schedules have been used during the years in PCa RT. Several randomized studies have shown that dose escalation improves biochemical control but is also followed by an increase in toxicity (57-59). Before the application of 3-dimensional conformal radiotherapy (3D-CRT) radiotherapy doses were usually about 64 Gray (Gy) in 2Gy fractions. With better techniques several randomized studies have shown that dose escalation (range74-80Gy) has a significant impact on 5 years biochemical progression free survival rate. The meta-analysis of randomized, controlled trials from Viani from 2009 (60) provided convincing evidence that high-dose RT is superior to conventional dose RT in terms of preventing biochemical failure in low-, intermediate-, and high-risk patients. They suggested that high-dose RT should be offered to all patients regardless their risk status. Some of the remaining questions are how high to escalate dose and what will the increased toxicity of dose escalation be in the era of IGRT. The actual recommendations from the European Association of Urology (EAU) guidelines working panel is a

minimum dose of 74Gy. Currently, standard treatment in most high volume centres consists of 75.6 to 81 Gy of radiation separated into 1.8-2 Gy fractions given daily during 7-9 weeks. The prolonged length of this standard prostate radiation coupled with advances in radiation therapy have stimulated interest in delivering more radiation per faction (consisting of fractions > 2 Gy) for the purpose of reducing overall treatment time and thereby improving patient convenience and possibly reduce increasing health care costs. This type of shorter treatment regime using larger doses of radiation per fraction is called hypofractionation (5;61).

Most tissue show a sparing effect of dose fractionation, so that the total doses for a given endpoint are higher if the dose is fractionated rather than when given as a single dose (62). Fractionated radiotherapy uses the differences in the DNA repair capacity of normal and tumour tissue. The alfa/beta ratio is a measure of the curvature of the cell survival curve and a measure of the sensitivity of a tissue to dose fractionation. It is also the dose at which the linear and quadratic components of cell killing are equal.

In fast growing tissue including many tumours, cells have little time to repair photon induced DNA damage. The α/β ratio is then typically around 10 Gy. In contrast, tissue with low renewal has a good opportunity for repair between fractions of irradiation. In such tissue, the α/β ratio is 3 Gy or lower. Slowly proliferating cells with low α/β ratio seems to be quite sensitive to an increased dose per fraction. PCa has an estimated α/β ratio of approximately 1.5 Gy, and hypofractioned regimes could be more efficient than conventional fractions of 1.8-2 Gy (63;64). Low α/β values (1.5 to 5 Gy) have been observed for late responding normal tissues, and there are concerns about potentially increased late bowel and urinary toxicity following hypofractionation (65-67).

3.7. TECHNICAL ASPECTS OF MODERN RADIOTHERAPY

Since 10 years the development of two major technologies; the intensity modulated radiation therapy (IMRT) and the image-guided radiotherapy have not only improved survival but it has also reduced toxicity after prostate radiotherapy even after dose-escalations above 72Gy (51).

3.7.1. IMAGE-GUIDED RADIOTHERAPY

The development of IGRT in prostate RT was reinforced after 2 studies showed that rectum distension during target planning simulation was

followed by a reduction in biochemical survival (68;69). Variations in patient setup, rectal air, stool volume and bladder filling create prostate position uncertainties both daily and even under treatment (8). Daily prostate displacements more of 10-15mm have been described in patients (70;71). The limited ability to control for the location of a tumour compromises the accuracy with which radiation can be delivered to tumour-bearing tissue. The following requirement for larger treatment volumes to accommodate target uncertainty restricts the radiation dose because more surrounding normal tissue is exposed. IGRT is based on repeated imaging during the course of radiotherapy. Out of multiple 2D images it is possible to construct a volumetric 3D image with soft tissue contrast. The created image is then registered to the planning CT this enables daily prostate position verification and patient setup correction. Using IGRT the treatment volumes can be optimized and tumouricidal doses can be delivered, achieving maximal tumour control with minimal complications. This reduction in setup uncertainties has been followed by a PTV margin reduction in many centres. Consequently several studies have reported about toxicity reduction obtained in several studies using modern EBRT (72;73). However, the today known IGRT technology does not eliminate the need for a margin. One study reports unexpected worse treatment outcome after the use of very narrow margins (74). There is still considerable scope for further improvement of IGRT systems. The ideal system would allow for precise daily imaging without significant extension of treatment time or patient exposure to additional radiation.

3.7.2. INTRAPROSTATIC FIDUCIAL MARKERS

Different types of gold markers with different length and diameter are used as standard intraprostatic fiducials markers. Minimum three gold markers are recommended to gain a triangulation that helps reposition the prostate in the three dimensions on 2D or 3D imaging. The use of the gold markers has increased both precision and accuracy of the EBRT but the markers also have some inconvenient. Positioning them is an invasive procedure with a non negligible risk of infection. They can migrate after their pose. The metallic artefacts they can create on the imaging may impair the visualisation of the contours of the prostate and impair correct delineation (51). Most commercialized gold markers today are not visible on T2 weighted MRI; the images most suitable for prostate delineation. The RT treatment modality evaluated in this thesis is based on insertion of a commercial Ni-Ti prostate stent (MemokathTM) as marker (75-77). Ti has

the atomic number 22, and is easily seen on x-ray images, which makes it suitable for x-rays positioning. Ti has an electron density relative to water of 3.7 and consequently good contrast is found using MV beam as well. The stent material is also non-magnetic and allows the use of the MR scanner on the patient with an inserted stent. The advantages compared to traditional gold markers are that the stent allows routinely co-registration of MRI and CT scans for treatment planning. It may be used for IGRT using both kV or MV or combinations. The size of the stent makes it a true 3D object, which allows calculations of both translation and rotation. The stent is removable using a flexible scope in an outpatient clinic setup.

Figure 4. Three different stent designs have been investigated during the past years. To the left is the Memokath, which was developed for treatment of benign prostate hyperplasia. In the middle is the DS-I stent. To the right is the DS-II stent, which is used in the present studies. All three designs are made of Ni Ti memory shape metal.

3.7.3. INTENSITY MODULATED RADIOTHERAPY

Intensity modulated radiotherapy (IMRT) allows better dose distribution with step dose-gradients during RT. Using IMRT the radiation intensity across the fields of the applied beams is modularly; the beam is continuously adapted to the contour of the target volume by a multileaf

colliminator and thereby, regulate the radiation intensity during delivery. This allows improved target conformity and coverage and reduced dose and volume to the normal tissue. The risk of using IMRT and a highly conformal radiation field is geometrical misses because of the sharp edges between the radiation field and the surrounding tissue. With dose escalation organ movements become a critical issue using IMRT. The IMRT treatment must be accompanied by accurate image guidance in some form of IGRT. Otherwise it could result in both severe under dosage of the PTV or unacceptable high dose delivery to the normal tissue (78). As well as prostate motion during treatment imposes further technical challenges exacerbated by longer treatment times required for IMRT compared with four-field treatment. The EAU guidelines refer to IMRT with or without image-guided radiotherapy as the gold standard for EBRT for prostate cancer, even though far from all centres can offer it today.

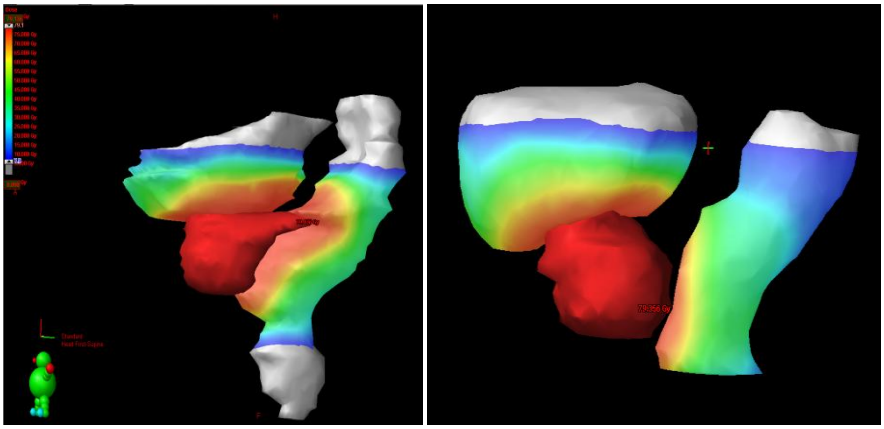

Figure 5. Examples of prostate cancer radiation fields with irradiation of the normal surrounding tissue.

3.8. ADJUVANT HORMONAL THERAPY

Androgen stimulation is mandatory for growth and survival of the PCa cells. Several randomized studies have established the indications for the combination of EBRT and androgen deprivation therapy (ADT) with regard to high–risk patients, as it increases overall survival (79-81). Whether this applies to all stages of prostate cancer is unclear. Some research suggests that ADT does not improve biochemical progression free survival in low

risk patients and intermediate risk-patients when adequate radiation doses are given. This is noted not only in patients treated with EBRT but also brachytherapy and surgery (82). Actual recommendations from the EAU guidelines are adjuvant hormonal therapy for a total duration of 3 years in patients with locally advanced disease. It must be mentioned though, that higher incidences of diabetes, cardiovascular disease, obesity and metabolic syndrome have been found in patients treated with long-term ADT (83).

3.9. OUTCOME AFTER RADIOTHERAPY FOR PROSTATE CANCER

EBRT technology has developed substantially the past decade, but so far no rapid impact on the mortality has been observed. The majority of PCa patients still die with their disease rather than of PCa, this is due to the advanced median age at diagnosis (70 years in Denmark in 2009 (84)) and prolonged natural history of early stage PCa. The majority of studies reporting on the treatment outcome after EBRT for PCa use more soft endpoints as biochemical failure or clinical failure rather that cancer specific survival; these "surrogate endpoints" are used because patients rarely die of prostate cancer. Unfortunately, when using such surrogate endpoints, other factors not connected to therapy like the frequency of PSA measurements may have dramatic effect on reported outcomes, and it can be difficult to compare different study results (85). Clinically relevant outcome measures include overall survival (OS), cancer-specific survival (CSS), biochemically progression free survival (BPFS), toxicity and QoL. Selected outcome data are presented in table III and IV.
Comparison of outcome data after EBRT for PCa must be done prudently because of the use of different treatment techniques, imaging, risk classification and patient characteristics. One recent reference study – the RTOG 9406 reported 5 year results of OS at 85%, CSS at 99% and BPFS at 80% (86).

Table IV. Radiotherapy outcome data.

Group	Year	Follow-up	RT-treatment	Dose (Gy)	Risk group	BPFS (%)	OS (%)	CSS (%)
Pervez (87)	2014	5 years	IMRT	86	high	91.7	86.7	-

Michalsky (86)	2012	5 years	3D-CRT	78	low	80	88	-
Wilcox (88)	2014	5 years	IG-IMRT	78	-	88	-	98
Takeda (89)	2012	5 years	IG-IMRT	80	interm	100	100	100
Takeda (89)	2012	5 years	IG-IMRT	80	high	82.2	91.7	100
Vassil (30)	2010	5 years	-	-	interm	85.7	-	-
Merino (32)	2013	5 years	IMRT	76	all	-	88.4	-
Widmark (90)	2009	10 years	3D-CRT	70	all	74.1	70.4	88.1

Treatment related toxicity is, also in the matter of PCa, known as the dose-limiting factor. Following the development in modern RT, toxicity levels have become very low. Data from recent studies are presented in table IV. A recent reference study from The Memorial Sloan-Kettering Cancer Center group has reported data on late toxicity from their experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66Gy and 81Gy, with a median follow-up of 10 years. Both acute gastrointestinal and genitourinary toxicity appeared to be predictive for corresponding late toxicity. The overall rate at follow-up of CTC-AE grade 2 or more gastrointestinal toxicity was 5% with IMRT versus 13% with 3D-CRT. The incidence of grade 2 or higher late genitourinary toxicity was 20% in patients treated with 81Gy versus 12% in patients treated with lower doses. The overall incidences of grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for genitourinary toxicity. The study underline that with dose escalation, genitourinary toxicity may become the predominant type of morbidity (91). A recent review on functional outcomes and complications from Budäus et al. from 2011 reported late gastrointestinal toxicity (RTOG scales ≥grade 2) from 3.1-29% and late

genitourinary toxicity (RTOG scales ≥grade 2 from 5.1-37% (92). Many factors are involved in the evaluation of toxicity and missing data on pre-treatment function, natural deterioration in sexual function with age in this patient group and missing data on co-morbidity are important confounders. Sexual morbidity in less reported in the literature. RT affects erectile function to a lesser degree that surgery, according to a retrospective analysis (93). One meta-analysis found a chance of 0.55 to preserve erective function 1 year after RT (94). Diabetes and ADT treatment have been reported as predictors for erective dysfunction (95). It is also known that LH-RH analog treatment can be followed by permanent sexual dysfunction (96).
In general it must be said that toxicity is difficult to compare and broad variation between studies are often seen. The major explanation of this variation if often differences in study design (e.g. prospective or retrospective data collection, lack of baseline recordings), different scoring scales (RTOG, CTC-AE, LENT-SOMA) and different information sources (patient or physician assessed toxicity). Information about study design and the collection of data should be described in details, and comparisons between studies should be done with care.

Table V. Selected toxicity outcomes after high dose RT. Recent studies using IGRT and/or IMRT. CTC-AE toxicity scores.

Group	Year	Follow-up	RT-treatment	Dose (Gy)	Risk Group	Urinary ≥grade2	GI ≥grade2	ED ≥grade2
Pervez (87)	2014	5 year	IMRT	68	high	19.4%	2.4%	-
Wilcox (88)	2014	5 year	IG-IMRT	78	interm-high	2.1%	3.4%	9.1%
Takeda (89)	2012	5 year	IMRT	76-80	interm-high	6.3%	6%	-
Zelefsky (97)	2012	3 year	IGRT	86.4	-	10.4%	1%	-

Tabel VI. Selected toxicity outcomes after high dose RT. RTOG toxicity scores.

Group	Year	Follow-up	RT-Treatment	Dose (Gy)	Risk group	GU ≥grade2	GI ≥grade2
Peeters (98)	2005	3 year	3D-CRT	78	interm-high	30.2	26.5
Pollack (99)	2002	6 year	CRT	78	all	10	26

Zietman (100)	2010	5 year	3D-CRT	79.2	-	29	25
Dearnaly (57)	2007	5 year	CRT	78	all	-	-
Sutani (101)	2015	3 year	IMRT	78	all	6.8	7.9

GU: genitourinary. GI: gastrointestinal. ED: erective dysfunction.

CHAPTER 4. ASPECTS OF RADIOBIOLOGY

The damaging effect of radiation therapy arises from its ability to ionize molecules in cells. The DNA is the critical target for radiation induced cell killing. Ionizing radiation causes both direct damage on DNA and indirect damage by producing free radicals that causes further DNA-damage. The cells die either an early cell death caused by the initial cellular damage or in the case of the majority of cells; a late cell death a relatively long time after irradiation; after failed attempts of cell proliferation (mitotic catastrophe).

The risk of radiation-associated injury of normal tissue is dependent of many factors like the volume of normal tissue irradiated, the total radiation dose delivered and the number of fractions delivered (dose per fraction). Pre- existing medical conditions and probably also genetics influence the risk of normal tissue damage too. The organs inherent sensitivity to radiation is yet another risk factor and is related to both cellular sensitivity and to microscopic and macroscopic anatomy. Cells of different tissues demonstrate different response rates to the same radiation dose. Early or late radiation response reflects different cell turnover rates. Rapidly dividing self-renewing tissues respond early to the effects of radiation; examples are skin, hair follicles, intestinal epithelium and bone-marrow. Late-responding tissues are tissues with a slow cell turnover like the spinal cord, lungs, bone and kidneys (102).

Radiation side effects may be induced in all normal cells and structures that are included in the treatment volume. Even the smallest volume the GTV, contains normal tissue elements like blood vessels and connective tissue

Normal tissues radiation sensitivity may significantly influence treatment planning and/or prescribed dose. The normal tissues at risk during RT are defined as organs at risk (OAR). The tissue radiation tolerance has been explained by Withers et al in 1988 on the base of functional subunits (FSUs). Per definition, a FSU is the minimum unit that can function independently of the remaining organ. The clinical consequence after radiation depends on the arrangement of FSUs within the exposed OAR. OARs are classified as serial, parallel, or mixed serial-parallel. In parallel organs, FSUs can be damaged without harming global organ function, since other regions maintain function. Examples are lung, liver and kidney. Typically, there is little effect on global organ function until a “critical volume” of the organ is affected, at which point, global organ function can

be impaired. The response of a parallel organ to radiation depends on the volume of affected organ (103).
In the matter of serial organs, the function of the entire organ depends on the function of each individual FSU; local damage to only one FSU can affect the whole organ and make it dysfunctional. This may be the case for nerves, intestines and oesophagus. The response of a serial organ to radiation is highly dependent on the maximum dose delivered to the organ. The dose distribution within the organ is of less relevance.
In reality most organs are not probably not either serial or parallel but to some degree mixed. The normal tissue reaction to radiation depends also on the endpoint. As an example considering the endpoint “stricture”, the bowel is considered a serial organ but considering the endpoint bleeding it is regarded as a parallel organ. OARs routinely considered during prostate RT are the bladder, rectum, penile bulb and femoral heads (102;103).
Dose-volume histograms (DVHs) (shown in figure 6) are histograms relating radiation dose to tissue volume in radiation therapy planning. In modern radiation therapy, 3D dose distributions are typically created in a computerized treatment planning system based on a 3D reconstruction of a CT scan. DVH summarizes 3D dose distributions in a graphical 2D format. The "volume" referred to in DVH analysis is a target of radiation treatment, a healthy organ nearby a target, or an arbitrary structure. DVH metrics correlate with patient toxicity outcomes
Normal tissue complication probability models (NTCP) have been made to try to predict the probability that a given radiation dose will lead to damage of normal tissue, based on the specific biological cells (i.e.organised in parallel, serial or combined FSUs). The NTCP models try to reduce complicated dosimetric and anatomic information to a single risk measure that can be used in a clinical setting. The NTCP estimates are population based, thus a low risk estimate does not exclude the occurrence of normal tissue injury, possibly severe in any individual patient (102).

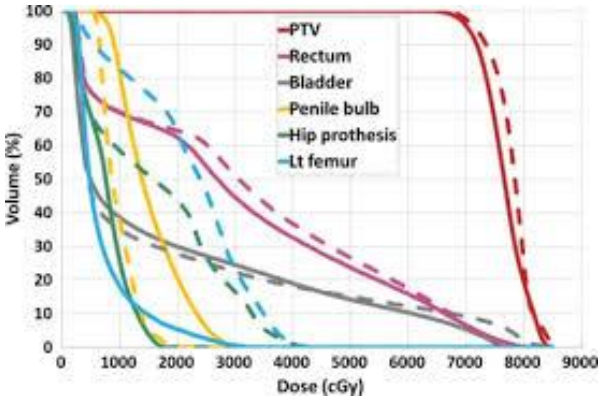

Figure 6: Dose-volume histogram. A DVH used clinically usually includes all structures and targets of interest in the radiotherapy plan, each line plotted a different colour, representing a different structure.

CHAPTER 5. AIMS OF THE PROJECT

The aim of this Ph.D. thesis was to explore a new treatment modality using MRI target planning and a Ni-Ti prostate stent as fiducial marker for both MR-CT co-registration and IGRT in prostate cancer RT. The thesis was planned as the long-term follow-up of this relatively new treatment set-up in search of better target planning before therapy and visualization during therapy; eventually to try to optimize treatment results but minimize treatment related side-effects. The scopes were:

- To evaluate 5 year follow-up in terms of survival, toxicity and QoL outcomes using a Ni TI prostate stent as fiducial marker.
- To evaluate MRI target delineation in prostate cancer compared to CT delineation in clinical practice.
- To assess 3 and 5 year toxicity and QoL in PCa patients after high-dose IGRT using MRI target delineation and the prostate stent as fiducial or standard CT delineation and standard gold markers as fiducials.
- To explore potential clinical and dosimetric risk factors for development of toxicity after EBRT.

CHAPTER 6. MATERIAL AND METHODS

In the following section the material and methods used in paper 1-4 will be briefly described. Detailed description of material and methods are presented in the individual papers. The scoring systems used in the studies are described in more details.

6.1. TOXICITY SCORING

Toxicity induced by prostate cancer treatments are typically expressed in the gastrointestinal or urinary tract. Urinary, bowel and sexual dysfunctions are often observed after treatment for EBRT for PCa and may impact on the patients' quality of life (104-106). Several questionnaires and scoring schemes have been used internationally to score prostate cancer treatment-related toxicity like the Radiation Therapy Oncology Group (RTOG), the Expanded Prostate Cancer Index, the Late Effects in Normal Tissue Subjective, Objective and Analytic scales (LENT SOMA), and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE). The different scoring systems with their variations in scoring scales and endpoints often make comparisons of toxicity from different study publications difficult. The RTOG score is widely used (57;58;91;99;104;105;107;108), but looses specificity when reporting toxicity while the score scheme summarizes the symptom scores into a single grade instead of keeping the different symptoms separate. Interesting and important information can be hidden in the single grade.
In the present studies toxicity was assessed primarily using the CTC-AE version 4.0 schemes. The National Cancer Institute defines an adverse event as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the treatment or procedure (109).
Grade refers to the severity of the adverse effect (AE). The CTC-AE displays Grades 1 through 5 with clinical descriptions of severity for each AE based on the following general guideline. A semi-colon indicates 'or' within the description of the grade.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Activities of Daily Living (ADL) are defined as the following:

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The rectal symptoms investigated in the studies were stool frequency, stool incontinence, rectal pain, proctitis, rectal pain and rectal bleeding. The urinary symptoms included frequency, urgency, incontinence, dysuria, urinary retention and haematuria. Late complications were defined as those developing ≥6 months after RT completion. Peak toxicity scores were registered, even in the case of full recovery.
Potential risk factors predicting both late gastrointestinal (GI) and genitourinary (GU) toxicity have been the subject to several studies. Concerning GI toxicity the symptom rectal bleeding is often studied, probably because of its objectivity but may not be the most annoying symptom (110). Different studies have described large rectal volume and dose, acute GI an GU toxicity, haemorrhoids, diabetes, advanced age, previous abdominal surgery, inflammatory bowel disease as risk factors (98;111-116).

With regard to GU toxicity large prostate volume, large radiation volume and dose, prior transurethral resection of the prostate (TUR-P) or bladder tumour (TUR-B) are recognized as risk factors (91;117;118).

6.2. QUALITY OF LIFE ASSESSMENTS

Historically, the management of cancer disorders has focused almost exclusively on the clinical outcome and clinician-reported measures of toxicity have been used to describe treatment side-effects. Today it has been recognized, that physician registered toxicity has the tendency to underestimate the impact of the symptoms (119). In recent years there has been an increased awareness that patient-reported outcomes like QoL are of great importance for men diagnosed with prostate cancer given that most men are diagnosed at an early stage and live for many years after treatment. Also due to the range of treatment options available with similar survival outcomes and the differential effects of various treatments on patients' symptoms and functional health, QoL assessment may play an even greater role in treatment decision-making for the prostate cancer patient than for some other types of cancer (120). Different questionnaires have been developed to assess health related (HR) QoL. The two probably best known questionnaires are the Functional Assessment of Cancer Therapy (FACT) – mostly used in the USA and the European Organization for Research and Treatment of Cancer (EORTC) – mostly used in Europe (121). The EORTC approach (122) includes a core questionnaire, the QlQ-C30 designed to measure physical, psychological, and social functioning of patients with cancer. It incorporates five functional scales (physical, role, cognitive, emotional, and social functioning); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and QoL scale. The remaining single items assess additional symptoms that are commonly reported by the patient: dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea and the perceived financial effect of the disease and treatment. The core questionnaire can be supplemented with a disease specific module, in the case of PCa: the QLQ-PR25 prostate module developed by the EORTC Genito-Urinary Tract Cancer Cooperative Group. This module consists of 25 questions and assesses urinary, bowel and sexual symptoms as well as symptoms related to hormonal treatment.
Each item scores from 1= not at all to 4= much, with the exception of the two overall QoL questions in the C30 questionnaire that scores from 1= very poor to 7= excellent. For ease of statistical interpretation and psychometric validation, all scale and item scores are linearly transformed

to a scale from 0 to 100. For the five functional scales and the global quality-of-life scale, a high score represents a good level of functioning. For the symptom scales and items, a high score corresponds to more severe symptoms.

6.3. PATIENT POPULATION

All patients included in the studies had biopsy verified localized or locally advanced PCa and were treated with IGRT at the department of Oncology, University Hospital of Aalborg from March 2007 to May 2009. The diagnosis and staging were performed at the local department of Urology prior to referral to the department of Oncology. The study population consisted of two groups of PCa patients. One group of 100 patients participated voluntarily in a phase 3 trial evaluating the NI-TI stent for MR-CT co-registration and as fiducial marker for IGRT (MR group) (76). Another consecutive group of 102 prostate cancer patients had standard planning CT and gold markers as fiducials during the same period (CT group). The patients were identified through searches in the patient radiation databases at the department of Oncology, Aalborg Hospital. Reasons for exclusion from toxicity and QoL assessments were death, biochemical failure (PSA nadir +2 ng/ml) and limited Danish skills. The exclusion of patients with biochemical failure was to avoid bias from either disease recurrence or salvage therapy. The assessments were made for the individual patient 3 and 5 years after their RT. Data regarding clinical and dosimetric parameters were retrieved from the hospital medical records.

6.4. RADIOTHERAPY TREATMENT

Patients had fiducials inserted in the prostate before dose planning imaging. Fiducials were either 3 gold markers or the Nickel-Titanium prostate stent. The gold markers were transrectally implanted. The prostate stent was endoscopically placed using local analgesics. Both procedures were performed at the local department of Urology.

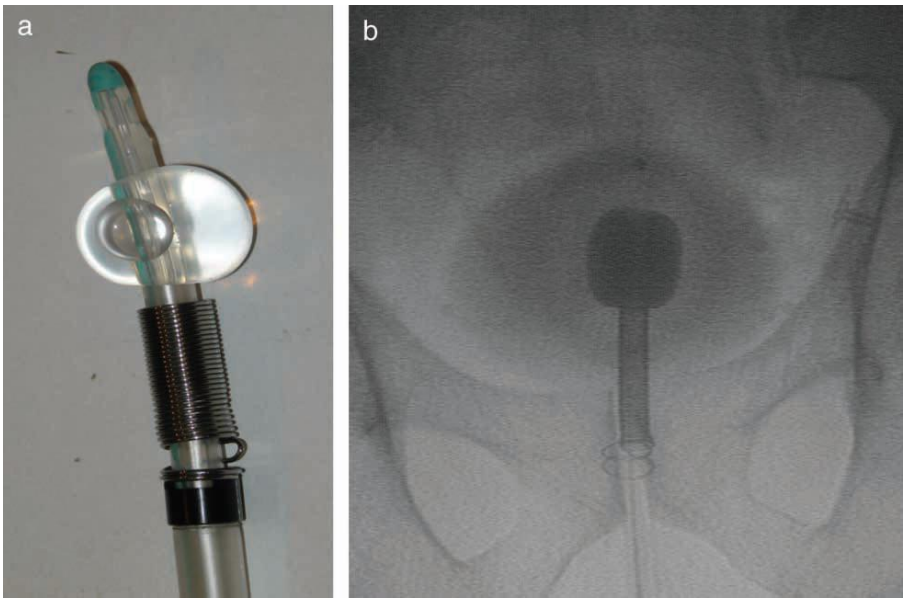

Figure 7.
a) The DS-II stent mounted on insertion kit and Foley catheter with balloon inflated.
b) Flouroscopy image from insertion. The Foley catheter is inflated with contrast media. The bladder is filled with diluted contrast media to give the contour of the bladder. The insertion kit has been pushed forward until the upper end of the stent touches the Foley catheter balloon. The distance from the lower end of the stent to the caudal part of the pubic bone has to match the measure from the diagnostic MR scan. The catheter has been flushed with hot water and the stent collar has expanded and locked the stent position in the prostate.

All patients had a planning CT scan (spiral scan slice thickness 2.5mm). Patients with the prostate stent inserted had an additional planning MR scan performed (1.5T or 3T MR T2 weighted images slice thickness 3mm, TR: 5320ms, TE: 94.96ms, FOV: 300x300mm^2, matrix: 382x224). The CTV was defined as the prostate gland. In case of seminal vesicle invasion or risk of invasion (Partin tables) (50), the CTV was defined as the prostate gland plus the proximal third part of the seminal vesicles. For patients in the CT group the CTV was outlined on the planning CT alone. Patients in the MR group had CTV outlined on the MR scan. The MR scan was co-registered to the planning CT using manually inserted landmarks on the inserted stent. The CTV outlined on MRI was subsequently copied to the planning CT

before dose calculation. A planning target volume (PTV) was created using an isotropic PTV to CTV margin of 5mm. Treatment planning was based on a 3D conformal technique with five conformal fields at gantry angles 0, 90, 140, 220 and 270 degree. Multi leave collimators were fitted until the 95% isodose encompassed the PTV. A dose of 2 Gy was prescribed to 100% isodose. Using 6 MV X-rays a total dose of 78 Gy was given in 39 fractions. The following constraints were used for normal tissue. Rectum V70≤25% (maximum 25% of the rectal volume should receive maximum 70Gy). V60≤50% and dorsal part of rectum received a maximum dose of 65 Gy. For the bladder V70≤35% and V60≤50% was used. For the femoral heads v52≤10% was used. Patients were treated lying supine with a knee and feet fixation. Using the inserted fiducials daily stereoscopic X-ray images were matched within 1-2 mm of CT reference digital reconstructed radiogram (DRR) images. After matching patients were automatically repositioned using the ExacTrac system with Robotics from Brainlab. The final position was verified daily using a new set of X-ray images before treatment was given.

6.5. STATISTICAL METHODS

Comparisons between participants and non-participants were made using the t-test or Mann-Whitney test for continuous variables and χ^2 or Fisher's exact test for categorical variables. These statistical tests were also used comparing patient characteristic and late toxicity scores between the CT and MRI treatment groups. We calculated time time-to-event curves from the end of RT, using Kaplan-Meier estimates. Log-Rank statistics was applied to test differences in survival and PSA-relapse free survival between the groups. The CT group was used as a reference when comparing the two treatment groups.

The possible correlation between rectal bleeding and each of the investigated clinical parameters was analyzed first by univariate (UVA) logistic regression analysis. After this a stepwise multivariate logistic regression model was build to analyse further those clinical and dosimetric parameters that appeared to be associated with the endpoint in the primary UVA. The association was defined as parameters with p-values ≤0.20. The odds ratio (OR) was used to express the strength of association of a parameter with the considered endpoint. QoL data was scored according to the EORTC scoring manual (122).

The p-values are two-sided, the significance level was set at 5%, 95% confidence intervals were calculated for the ORs. All analyses were carried

out using the statistical software package from Stata v.11 (Stata statistical software version 11; Stata Corporation).

CHAPTER 7. RESULTS

A short summary of the results from the four papers are presented in the following. A detailed description of the results is presented in the individual papers 1-4.

Paper 1

MRI target delineation may reduce long-term toxicity after prostate cancer radiotherapy.

Sander L, Langkilde NC, Holmberg M, Carl J

Acta Oncologica 2014

Summary
Aiming for minimal toxicity after PCa RT, MRI delineation could be a possible tool, knowing that CTV are up to 30% smaller on MRI delineation compared to CT delineation. The study evaluated toxicity 3 years after high-dose IG-RT comparing target planning delineation on MR and a prostate stent as fiducial with CT target planning and the use of gold markers as fiducials. The treatments were performed with the same radiation dose and PTV margins. A significantly smaller CTV was found in the MR-group (40.9 vs. 52.1. cm^3). The CTV was correlated to a reduction in overall rectal toxicity, but not to a reduction in overall urinary toxicity.
In general the late side effects 3 years after RT were few and mild and comparable with the lowest toxicity rates reported in the literature. No grade 3 toxicity was found. Significantly lower urinary frequency and urinary retention toxicity scores were observed following MRI delineation. No significant differences were found in overall urinary or rectal toxicity.

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ORIGINAL ARTICLE

MRI target delineation may reduce long-term toxicity after prostate radiotherapy

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ABSTRACT

Background and purpose. Aiming for minimal toxicity after radical prostate cancer (PC) radiotherapy (RT), magnetic resonance imaging (MRI) target delineation could be a possible benefit knowing that clinical target volumes (CTV) are up to 30% smaller, when CTV delineation on MRI is compared to standard computed tomography (CT). This study compares long-term toxicity using CT or MRI delineation before PC RT.

Material and methods. Urinary and rectal toxicity assessments 36 months after image-guided RT (78 Gy) using CTC-AE scores in two groups of PC patients. Peak symptom score values were registered. One group of patients (n = 72) had standard CT target delineation and gold markers as fiducials. Another group of patients (n = 73) had MRI target delineation and a nickel-titanium stent as fiducial.

Results. At 36 months no difference in overall survival (92% in both groups, p = 0.29) or in PSA-relapse free survival was found between the groups (MRI = 89% and CT = 94%, p = 0.67). A significantly smaller CTV was found in the MRI group (p = 0.02). Urinary retention and frequency were significantly reduced in the MRI group (p = 0.03 in the matter of both). The overall urinary and rectal toxicity did not differ between the two groups.

Conclusion. MRI delineation leads to a significantly reduced CTV. Significantly lower urinary frequency and urinary retention toxicity scores were observed following MRI delineation. The study did not find significant differences in overall urinary or rectal toxicity between the two groups. PSA-relapse survival did not differ between the two groups at 36 months.

Radiotherapy (RT) plays a key role in today's treatment of prostate cancer (PC). In several randomised trials dose escalation has shown to improve the biochemical control, but it is also followed by an increase in toxicity [1–3]. RT-related toxicity in PC most commonly involves the urogenital and gastrointestinal systems. Development of these toxicities is related to both the radiation dose to and the volume of normal tissue irradiated during the therapy [4,5]. Day-to-day changes in patient position and variations in prostate position during the course of radiation are considered as sources of treatment errors. Prostate displacements of more than 10–15 mm have been documented [6]. To account for these positional changes a margin is added to the clinical target volume (CTV) to assure sufficient dose coverage of the targeted tumour volume. This, however, increases the risk of over dosage of normal tissue and thereby toxicity. The use of prostate markers enables a more exact target location and makes margin reduction possible [7]. Novel techniques like daily image-guided radiotherapy (IGRT) are widely used combined with prostate fiducials for daily prostate position verification and correction. This has led to a reduction in the observed toxicity [8,9].

Currently, the most used method is implanted gold markers (GM) combined with treatment planning on computed tomography (CT). This method, however, has been shown to lead to an overestimation of the prostate volume. Volumes up to 30% larger have been found on CT when compared to target delineation on MRI [10–12]. CT-MRI image

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fusion-based treatment planning allows more accurate prediction of the target volume [13,14]. The CT-MRI co-registration can be done in several ways – on bony landmarks, with endorectal coil or by intraprostatic fiducial markers. Despite this, MRI-based planning has not yet replaced CT planning for routine PC RT. Studies are needed to evaluate whether the reduction in CTV on MRI is followed by a clinical relevant reduction in the long-term toxicity without compromising treatment failure.

The aim of this historical follow-up study was to evaluate the late (36 month) urinary and rectal toxicity among men with localised or locally advanced PC treated with RT at the Department of Oncology, Aalborg University Hospital between 2007 and 2009. Comparisons were made between the standard treatment (planning CT/GM) and a new treatment modality using MRI delineation, CT-MRI co-registration and a Nickel-Titanium (Ni-Ti) stent as prostate marker [15].

Material and methods

Patient population

Included in this non-randomised historical follow-up study were patients with localised or locally advanced PC (T1-T3N0M0) who completed RT with curative intent at the Department of Oncology, Aalborg University Hospital between March 2007 and May 2009. During this period, a group of 100 patients participated voluntarily in a phase III trial evaluating a Ni-Ti stent for MRI-CT co-registration and as fiducial marker (MRI-group) [15]. Another consecutive group of 102 PC patients had standard planning CT and GMs as fiducials during the same period (CT-group).

The patients were identified through searches in the patient radiation databases at the Department of Oncology, Aalborg Hospital.

Reasons for exclusion were death, biochemical failure (PSA nadir + 2 ng/ml) and inability to read and understand the questionnaires in Danish. The study was approved by the Regional Committee for Medical Research Ethics.

Toxicity assessment

All eligible men received a mailed invitation to participate in the study including information about the study, a consent form and a questionnaire. All participants completed and returned the consent form and questionnaire in a prepaid envelope.

The patients that returned the consent form and questionnaire were contacted for a telephone interview and toxicity regarding urinary and rectal symptoms was assessed. All the patients were contacted by one doctor or one research nurse.

The late toxicity assessment was made for the individual patient three years after his RT. Late complications were defined as those developing ≥ 6 months after RT completion. Peak toxicity scores were registered, even in the case of full recovery. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0. Rectal symptoms included stool frequency, stool incontinence, rectal pain, proctitis, rectal pain and rectal bleeding. Urinary symptoms included frequency, urgency, incontinence, dysuria, urinary retention and haematuria.

Data regarding clinical parameters like Gleason score, tumour stage, presenting PSA level, prostate volume, medications and co-morbidity (including haemorrhoids) were retrieved from the medical hospital records.

Treatment

Men with medium and high risk disease according to the D'Amico classification [16] received neo-adjuvant endocrine treatment with either LHRH analogues or non-steroidal anti-androgens for three months before irradiation. Endocrine treatment was continued during irradiation and for a limited period thereafter, usually for one year according to the recommendations in Denmark at that time.

Patients had fiducials inserted in the prostate before dose planning imaging. Fiducials were either three GMs or a Ni-Ti prostate stent. All patients had a planning CT scan (spiral scan slice thickness 2.5 mm). Patients with the prostate stent inserted had an additional planning MRI scan performed (1.5T or 3T MR T2 weighted images slice thickness 3 mm, TR: 5320 ms, TE: 94.96 ms, FOV: 300×300 mm^2, matrix: 382×224). The CTV was defined as the prostate gland. In case of seminal vesicle invasion or risk of invasion (Partin tables) [17], the CTV was defined as the prostate gland plus the proximal third part of the seminal vesicles. For patients in the CT group the CTV was outlined on the planning CT alone. Patients in the MRI group had CTV outlined on the MRI scan. The MRI scan was co-registered to the planning CT using manually inserted landmarks on the inserted stent. The CTV outlined on MRI was subsequently copied to the planning CT before dose calculation.

A planning target volume (PTV) was created using an isotropic PTV to CTV margin of 5 mm. Treatment planning was based on a 3D conformal technique with five conformal fields at gantry angles 0, 90, 140, 220 and 270 degree. Multi leave collimators were fitted until the 95% isodose encompassed the PTV. A dose of 2 Gy was prescribed to 100% isodose. Using 6 MV x-rays a total dose of 78 Gy was given in 39 fractions. The

following constraints were used for normal tissue. Rectum V70 ≤ 25% (maximum 25% of the rectal volume should receive maximum 70 Gy). V60 ≤ 50% and dorsal part of rectum received a maximum dose of 65 Gy. For the bladder V70 ≤ 35% and V60 ≤ 50% was used. For the femoral heads v52 ≤ 10% was used. Patients were treated lying supine with a knee and feet fixation. Using the inserted fiducials daily stereoscopic x-ray images were matched within 1–2 mm of CT reference digital reconstructed radiogram (DRR) images. After matching patients were automatically repositioned using the ExacTrac system with Robotics from Brainlab. The final position was verified daily using a new set of x-ray images before treatment was given.

Statistical methods

Comparisons between participants and non-participants were made using the t-test or Mann-Whitney test for continuous variables and χ^2 or Fisher's exact test for categorical variables. These statistical tests were also used comparing patient characteristic and late toxicity scores between the CT and MRI treatment groups. We calculated time time-to-event curves from the end of RT, using Kaplan-Meier estimates. Log-rank statistics was applied to test differences in survival and PSA-relapse free survival between the groups. The CT group was used as a reference when comparing the two treatment groups. P-values are two-sided and statistical significance was set at 5%. Univariate and multivariate logistic regression was used for subgroup analysis. The data were analysed using STATA v11 (Stata statistical software version 11; StataCorp).

Results

Two hundred and two patients underwent curatively intended RT during the defined period. A total of 145 men returned the consent form and participated in the study. There were no significant differences between participants and non-participants with regard to patient characteristics or tumour characteristics except that T-stages were higher in the group of participants (p = 0.05) (data otherwise not shown). Patient flow is shown in Figure 1.

Follow-up time for all participants was 36 months. Baseline patient characteristics are presented in Table I. The two groups were comparable in the matter of age, Gleason score, pre-treatment PSA, inclusion of seminal vesicles in CTV, smoking, diabetes and medications. Higher T-stages and risk classification were present in the MRI group. No significant difference in overall survival was found at 36 months (CT group = 92% and MRI group = 92%, p = 0.29). The PSA failure free survival did not differ significantly either (CT group = 94% and MRI group = 89%, p = 0.67).

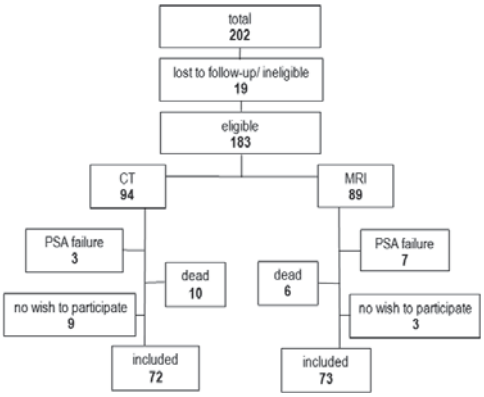

Figure 1. Patient flow. Fourteen were lost to follow-up (11 from the Faroe Islands, three from other Danish regions). Ineligible were two patients because of non-standard RT treatment, two because of language problems, one because of PSA failure during RT (metastatic disease). PSA failure = nadir + 2 ng/ml.

The prostate volume was found to be 21.5% smaller in the MRI group than in the CT group with mean volumes of 40.9 cm^3 and 52.1 cm^3, respectively (p = 0.02). In general the late side effects within the first three years after RT were few and mild in both groups. No grade 3 toxicity was registered. The results for the peak toxicity scores concerning rectal and urinary symptoms are presented in Tables II and III, respectively. Comparisons between the maximum overall scores of late rectal and urinary toxicities observed are made in Table IV, these do not differ significantly between the groups (p = 0.4 and 0.5, respectively).

With regard to rectal symptoms, grade 2 toxicity was registered only concerning "rectal bleeding" and in only four patients in total. The one patient from the MR group with grade 2 rectal bleeding was subsequently diagnosed with ulcerative colitis subsequent the RT. No significant differences were found concerning rectal symptoms between the two groups. There was no influence of age, T-stage, Gleason score, pre-treatment PSA, seminal vesicles irradiation, anticoagulants, smoking or statin-use on the development of rectal symptoms.

Urinary toxicity was predominantly manifested as increased frequency and urgency symptoms requiring α-blocker medications. No difference in overall urinary toxicity was found. Looking at the specific toxicity a statistically significant difference between the two groups was found with respect to "frequency" and "urinary retention" (p = 0.03 in the matter of both). No correlation was found between overall urinary toxicity and CTV. No apparent influence of age, T-stage, Gleason score, pre-treatment PSA, anticoagulants, smoking or

Table I. Patient characteristics.

	MRI	CT	
Age (range)	70.5 (62–80)	70.1 (58–78)	p = 0.5
T-stage (%)			
T1	9 (12)	26 (36)	p = 0.003
T2	28 (38)	14 (19)	
T3	36 (49)	31 (43)	
T4	0	1 (1)	
Gleason score (%)			
6	11 (15)	3 (4)	p = 0.19
7	52 (71)	58 (81)	
8	5 (7)	6 (8)	
9	4 (5)	5 (7)	
10	1 (1)	0	
Risk (d'Amico classification) (%)			
Low	4 (5)	1 (1)	p = 0.02
Intermediate	18 (25)	33 (46)	
High	51 (70)	38 (53)	
Pretreatment PSA			
Mean (range)	15.5 (4.1–67)	14.6 (0.6–67)	p = 0.23
Seminal vesicles in CTV (%)	9 (12)	10 (14)	p = 0.78
Hormonal therapy (%)	69 (95)	69 (96)	p = 0.19
Nicotine (%)	17 (23)	15 (21)	p = 0.79
Diabetes (%)	10 (14)	11 (15)	p = 0.44
Use of antikoagulantia (%)	10 (14)	9 (13)	p = 0.83
Haemorrhoids (%)	5 (7)	4 (6)	p = 0.75
Medications			
No drugs	12 (16)	13 (18)	p = 0.92
<5 different drugs	45 (62)	42 (58)	
Polyfarmaci (≥ 5)	16 (22)	17 (24)	

diabetes on the development of urinary symptoms was seen.

Discussion

To our knowledge, this is the first report to compare toxicity in patients with localised or locally advances PC treated with IGRT using target planning delineation on either MRI or CT. The comparison is of value in that both groups were treated with the same radiation dose and with similar margins for the PTV. The difference between the two groups, were whether the target planning was based on MRI or CT delineation and whether a three-dimensional Ni-Ti stent or three GMs were used as fiducials for daily positioning verification. We observed, as expected, a smaller CTV volume in the MRI-delineated prostates. The CTV was correlated to a reduction in overall rectal toxicity but not correlated to a reduction in overall

Table II. Rectal toxicity.

	Grade	MRI	CT	Total	
Diarrhoea	0	68	63	131	p = 0.3
	1	5	9	14	
	2	0	0	0	
Faecal incontinence	0	68	68	136	p = 0.7
	1	5	4	9	
	2	0	0	0	
Proctitis	0	68	67	135	p = 0.9
	1	5	5	10	
	2	0	0	0	
Rectal bleeding	0	53	44	97	p = 0.3
	1	19	25	44	
	2	1	3	4	
Rectal pain	0	73	72	145	
	1	0	0	0	
	2	0	0	0	

Table III. Urinary toxicity.

	Grade	MRI	CT	Total	
Haematuria	0	66	67	133	p = 1.0
	1	6	5	11	
	2	1	0	1	
Frequency	0	47	36	83	p = 0.03
	1	16	30	46	
	2	10	6	16	
Urinary retention	0	70	61	131	p = 0.03
	1	3	11	14	
	2	0	0	0	
Urethral pain	0	69	70	139	p = 0.7
	1	4	2	6	
	2	0	0	0	
Urgency	0	40	43	83	p = 0.7
	1	23	21	44	
	2	10	8	18	
Incontinence	0	68	66	134	p = 0.9
	1	5	5	10	
	2	0	1	1	

Table IV. Late overall rectal and urinary toxicity.

Grade	MRI (n = 73)		CT (n = 72)		p-value
	n	%	n	%	
Rectal					
0	46	63	39	54.1	0.4
1	26	35.6	30	41.7	
2	1	1.4	3	4.2	
Urinary					
0	29	39.7	25	34.7	0.5
1	32	43.8	38	52.8	
2	12	16.4	9	12.5	

urinary toxicity. However, the number of patients that experienced urinary frequency and urinary retention differed significantly between the two groups. The overall incidences of both late rectal and urinary toxicities showed a trend towards less toxicity in the MRI group though not significant.

Late grade 2 urinary toxicity was observed in 16.4% (MRI) and 12.5% (CT) of the patients. These results are consistent with the results in resent publications like those of Zelefsky (10.4%, IGRT, 86.4 Gy) [18] and Crehange (7%, IMRT, 74–78 Gy) [19]. With regard to late grade 2 rectal toxicity our findings at 1.4% (MRI) and 4.2% (CT) are also comparable with Zelefsky (1%) and Crehange (1.2 %).

The contouring variation seen with MRI is lower than with CT because of the superior distinction of the prostate from adjacent structures on MRI. However, with training, these structures can many times be recognised on CT scans as well [11]. This may explain that we have found a difference of "only" 21.5% between the MRI-delineated prostate volumes and the CT-delineated volumes, whereas others have found differences above 30%. The similar toxicities between the two groups found in this study may also be a result of this.

Albeit we did not observe a reduction in late rectal toxicity, this might be explained by the low rectal toxicity incidence with IGRT in general. A larger patient population would be required to demonstrate a difference in rectal toxicity between the groups. The strong correlation between CTV and rectal bleeding and the finding of a smaller CTV in the MRI group in this study sustain this theory. Other studies have evaluated rectal dose-volume histograms and found consistent results on the dose-volume effect on the probability of developing rectal bleeding [20,21]. Both the absolute and the percentage of rectal volume receiving the highest doses (>60 Gy) are correlated with rectal bleeding [22]. As the CTV increases a larger volume of the rectum is at risk of high dose irradiation thus explaining the increased risk of rectal bleeding.

There is a delicate balance between the aim of maximum accuracy and PTV margin reduction to avoid normal tissue toxicity, and the risk of missing microscopic extra prostatic tumour extension as consequence of irradiated target volume reduction. The exact incidence and extent of microscopic disease remains uncertain because of imaging modalities limitations, but is known to be correlated with certain pre-treatment characteristics like PSA, T-stage and Gleason score [23]. A recent study from Heemsbergen et al. [24] has reported fewer clinical failures for high-risk PC patients treated with rectangular fields, compared to conformal fields underlining the above mentioned problem. Patient recruitment took place in the period 1994–1996, thus in another era. Imaging modalities have improved significantly since and androgen deprivation therapy in combination with RT is standard treatment of high-risk PC patients today. However, the authors raise a relevant question: Maybe margins can be too tight, thus compromising clinical failure and in the end survival. In that case higher toxicity rates would be acceptable, if the patients gain in terms of prolonged survival.

Limitations of this study include the relatively short follow-up time and that it is a historical follow-up design. A prospective design, especially with baseline assessments before RT, would be preferable to evaluate changes in late toxicity. In the matter of long-term toxicity registrations, some of the symptoms may be due to undetected co-morbidity progression. This may be particularly relevant in an elderly patient population like PC patients. Age-matched control groups are known to be affected by significant urinary problems [25]. These considerations are, however, of less significance in this study, as we compared two patient groups with similar baseline assessments.

This study includes a relatively low number of patients. Furthermore, we observed a very low number of patients with ≥ grade 2 toxicity, and this limits the statistical power.

MRI delineation and MRI-CT co-registration is today feasible as part of IGRT treatment for PC. We have presented the first data from our institution reporting 36-month toxicity after RT using MRI delineation for target planning. The effect of MRI delineation will require further confirmation with future prospective studies on more patients with longer follow-up time to evaluate the clinical relevance in terms of possible toxicity reduction. MRI delineation using the stent as fiducial is a costly and time consuming procedure, and therefore only recommendable if relevant toxicity reduction is obtained.

Future perspectives using the Ni-Ti stent as fiducial might also include sparing of the urethra. Dose exposure to the urethra and bladder neck attributes to the urinary toxicities. Urethra sparing with IMRT have so far been considered controversial because of

concerns for under dosage of the periurethral tissue. A theoretical study suggests preserved tumour control using the Ni-Ti stent as fiducial combined with IMRT [26].

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Paper 2

Clinical and dosimetric parameters influencing on rectal bleeding after radiotherapy for prostate cancer.

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Manuscript under revision

Summary
The potential correlation between different clinical and dosimetric parameters and the symptom “rectal bleeding” was investigated in the total study population. This was done by univariate and multivariate logistic regression analyzes. Toxicity results 3 years after RT was used. Analyzes were made for grade ≥1 rectal bleeding due to a very low number of grade 2 rectal bleeding (4 patients). A cumulative incidence of 33% was found.
Dmax, Dmean, Dmin2cc, V60Gy, V72Gy, smoking, T-stage, age and CTV seemed to be correlated with the endpoint at the UVA. The final MVA showed a robust statistically significant correlation between rectal bleeding and CTV (OR=1.01 per unit change, p=0.03). The potential correlation disappeared for the other investigated parameters.
Of the parameters analyzed in this study, increasing CTV was found to be the only really robust predictor for late rectal bleeding with odds ratio of 1.01 per unit change.

Clinical and dosimetric parameters influencing on rectal bleeding after radical radiotherapy for prostate cancer.

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Keywords
Prostate cancer – clinical risk factors – dosimetric risk factors - rectal bleeding

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Clinical and dosimetric parameters influencing on rectal bleeding after prostate radiotherapy

Abstract

Introduction:
The aim of this study was to evaluate the role of different clinical and dosimetric parameters influence on late rectal bleeding after prostate cancer radiotherapy.

Materials and methods:
Toxicity was assessed 36 months after radical prostate radiotherapy (78Gy/39f) in 145 patients treated at the Hospital of Aalborg between May 2007 and May 2009. Toxicity was recorded using Common Terminology Criteria for Adverse Events for rectal bleeding. Analyzes were made for grade ≥1 toxicity. The correlation between different clinical and dosimetric parameters was investigated by univariate (UVA) and multivariate (MVA) logistic regression analyzes.

Results:
A cumulative incidence of 48/145 (33%) was found. CTV was found to be correlated with rectal bleeding at UVA (OR=2.57 per unit change, p=0.01). Among the other parameters only age and smoking appeared to be associated with rectal bleeding (OR=0.94 per year, p= 0.08 and OR=0.39, p= 0.06, respectively) at UVA. MVA showed a statistically significant correlation between rectal bleeding and CTV (OR=2.96, p=0.01), smoking (OR=0.35, p=0.04) and age (OR=0.9, p=0.01).

Conclusion:
At 3 years a cumulative incidence of 33% was observed for grade 1-2 rectal bleeding. The analysis highlighted CTV as a major risk factor. Smoking showed a protective effect against the development of rectal bleeding. There seemed to be a discrete protective effect of age. The other clinical factors: BMI, pre-treatment PSA, diabetes, cardiac heart disease, poly-farmacia and anti-coagulants seemed to have no predictive power.

Article text:

Introduction:
Despite advances in prostate cancer (PC) radiotherapy (RT) techniques e.g. the use of 3D conformal radiotherapy and image-guided RT (IGRT), a significant proportion of patients still suffer from long-term RT-induced gastrointestinal (GI) symptoms [1,2]. These symptoms include rectal bleeding, stool frequency, proctitis and fecal incontinence, symptoms that are known to influence patient satisfaction and quality of life [3,4]. Rectal bleeding has been one of the most studied endpoints after external RT for prostate cancer probably because of its frequency and objectivity. Late injury of the rectum most often occurs within the first 2-4 years [5] after treatment. The origin of the lesion that results in rectal bleeding is poorly understood and unlike many other late complications, which persist or progress, rectal bleeding can fluctuate and even resolve spontaneously [6]. But even as a single event, an episode with rectal bleeding can influence on the patient's quality of life and cause significant anxiety.
Several studies have described a dose-response relationship concerning dosimetric factors like total dose, dose per fraction, volume irradiated and irradiation site and the development of rectal toxicity [5,7,8]. There is a growing recognition that individual clinical parameters like age, BMI, co-morbidity, medication and smoking history can influence the toxicity risk. Identification of the relevant parameters and incorporation of these into dose-volume based models will most probably improve the prediction of toxicity.
It has been hypothesised that variation in late toxicity between individuals may be due to genetic variation [9]. Exploring such potential genetic factors it will be necessary to know and adjust for potential non-genetic risk factors. For patients who receive radiotherapy, prediction of late toxicity may help in introducing preventive procedures or planning corrections to better individualise the treatment to avoid toxicity.
The aim of this study was to evaluate the role of different clinical and dosimetric parameters influence on late rectal bleeding after external RT for prostate cancer (PC).

Clinical and dosimetric parameters influencing on rectal bleeding after prostate radiotherapy

Material and methods:

Patient population

A total of 202 patients with localised or locally advanced PC (T1-T3N0M0) were treated with radical RT at the department of Oncology, Aalborg University Hospital between March 2007 and May 2009. For the purpose of this study data were retrieved from a non-randomized historical follow-up study looking at toxicity and quality of life after radical RT focusing on MRI versus CT target delineation for RT dose planning on this patient group. Final analyzes refereed to 145 patients (reference til egen artikel!) The toxicity data on rectal bleeding were used in this study. The study was approved by the Regional Committee for Medical Research Ethics in accordance with the Helsinki Declaration II.

Radiotherapy technique

Men with intermediate and high risk disease according to the D'Amico classification [10] received neo-adjuvant endocrine treatment with either luteinizing hormone-releasing hormone analogues or non-steroidal anti-androgen for 3 month before irradiation. Endocrine treatment was continued during irradiation and for a limited period thereafter, usually for 1 year according to the recommendations in Denmark at that time. Patients had fiducials inserted in the prostate prior to dose-planning imaging was performed. Fiducials were either gold markers or a Nickel-Titanium prostate stent. The prostate stent was removed 3 months after radiotherapy. The clinical target volume (CTV) was defined as the prostate gland. In case of seminal vesicle invasion or risk of invasion (Partin tables) [11], the CTV was defined as the prostate gland plus the proximal third part of the seminal vesicles. A planning target volume (PTV) was created using an isotropic PTV to CTV margin of 5mm. Treatment planning was based on a 3D conformal technique with five conformal fields. A dose of 78 Gy was given in 39 fractions in total. The department's standard constraints were used (rectum V70<=25%, V60<=50% and dorsal part of rectum Dmax<65 Gy). The rectum was defined and delineated from just above the anal verge to the recto-sigmoid flexure. IGRT was performed using the inserted fiducials and daily stereoscopic X-ray images, matched within 1-2mm of CT reference digital reconstructed radiogram (DRR) images. Patients were automatically positioned using the ExacTrac system with Robotics from Brainlab. The final position was verified using a new set of X-ray image before treatment was given.

Clinical endpoint

In this analysis the incidence of late rectal bleeding was the clinical endpoint. Bleeders were defined as patients with ≥ grade 1 bleeding at any time after 6 months after radiotherapy completion, even in the case of full recovery.

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Grade 1: mild; intervention not indicated. Grade 2: moderate symptoms, medical intervention or minor cauterization indicated. Grade 3: transfusion, radiologic, endoscopic, or elective operative intervention indicated.

Data was collected by one doctor or one research nurse during a telephone interview or were retrieved from the hospital medical records. Clinical parameters considered were Gleason score, tumour stage, pre-treatment PSA, prostate volume (CTV), age, BMI, seminal vesicles irradiation, co-morbidities (e.g. diabetes and cardiac heart disease), smoking (during radiotherapy), poly-farmacia (>5 different medications) and the use of anti-coagulants. The dosimetric parameters considered for each patient were rectal volume, maximum and mean rectal distribution doses, the percent fraction of the rectum receiving more than 60 and 72GY (named V60 and V72) and the minimal dose given to the rectal area of 5cm³ that received the highest total dose (named Dmin2cc).

Statistics

The possible correlation between rectal bleeding and each of the investigated clinical parameters was analyzed first by univariate (UVA) logistic regression analysis. After this a stepwise multivariate logistic regression model was build to analyse further those clinical and dosimetric parameters that appeared to be associated with the endpoint in the primary UVA. The association was defined as parameters with p-values ≤0.20.

The odds ratio (OR) was used to express the strength of association of a parameter with the considered endpoint. The p-values are two-sided, the significance level was set at 5%, 95% confidence intervals were calculated for the ORs. All analyses were carried out using the statistical software package from Stata v.11 (Stata statistical software version 11; Stata Corporation)

Results:
Patient characteristics are shown in table 1. None of the patients had symptoms of rectal bleeding before radiotherapy. No grade 3 or worse late toxicity have been observed. Concerning grade 1 or 2 rectal bleeding we found a cumulative incidence of 44 patients with grade 1 and only 4 patients with grade 2 within 3 years after RT. Due to the low number of patients with grade 2 toxicity statistical analysis were made for the clinical outcome ≥ grade 1 toxicity. A cumulative incidence of 48/145 (33%) was found for this outcome within 3 years after RT.
The results from the primary UVA analysis are shown in table 2. Parameters that appeared to be associated with the outcome at the primary UVA was age, smoking, t-stage, CTV, Dmax, Dmean, Dmin2cc, V60Gy and V72G. In the subsequent MVA including the mentioned parameters from the UVA only CTV (OR=1.01, p=0.03) and age (OR=0.91, p=0.03) was found to be correlated with rectal bleeding (table 2). None of the other parameters showed even borderline significance. The association found at the UVA concerning the dosimetric parameters disappeared for all of them, when adjusting for the CTV. We looked at eventual outliers to check for the robustness of the multivariate regression model. When we did the MVA dropping the 2 youngest patients (both 55 years old), age does not show any significant association with rectal bleeding (OR=0.93, p=0.08). The CTV was the only really robust parameter that seemed correlated with the outcome.

Discussion:
The impact of clinical and dosimetric parameters as predictors of late rectal bleeding has been emphasised in recent literature.
In this study we found a cumulative incidence of ≤ grade 1 rectal bleeding, 3 years after RT at 33%. This is comparable with the results of Koper, also reporting a 3 years cumulative incidence of rectal bleeding of 33% [12].
Of the parameters analyzed in this study, increasing CTV was found to be the only really robust predictor for late rectal bleeding with odds ratio of 1.01 per unit change (p=0.03). Several other studies have evaluated rectal dose-volume histograms and found consistent results of the dose-volume effect on the probability of developing rectal bleeding [5,12-15]. Both the absolute and the percentage of rectal volume receiving the highest doses (>60Gy) have been correlated with rectal bleeding. We found the same correlation in the UVA with regard to the parameters min2cc, V60Gy and V72Gy in the UVA. This correlation disappeared when adjusting for the CTV, leaving only the CTV to be significantly correlated with rectal bleeding in the final MVA. As the CTV increases a larger volume of the rectum is at risk of high dose irradiation thus explaining the increased risk of rectal bleeding. The dose-volume data were calculated from one planning CT scan only, and we had no standard recommendations with regard to the rectal filling during RT. The rectum most probably has had different volumes during the 39 RT sessions for each patient and as a result the delivered rectal doses can differ significantly from the planned doses. This is probably one of the reasons why the correlation with regard to the dose-volume data disappears in the MVA. The CTV is, on the contrary, a consistent volume.
Clinical factors that have been found to contribute to the degree of rectal bleeding after radical prostate radiotherapy include previous abdominal surgery, hemorrhoids, pre-existing diabetes mellitus, smoking, BMI, inactivity and age [12,15-21].
In the primary UVA smoking seemed correlated with rectal bleeding (p=0.06), controversially showing a protective effect against rectal bleeding after radiotherapy. This correlation disappears in the multivariate analysis. But we found one earlier study describing the same correlation [12]. They found an association between smoking and less rectal bleeding (p=0.08) and report rectal blood loss for 37% of the non-smokers and 14% of the smokers. In our study the percentages were 37% (42/113) for non smokers and 18% (6/32) for smokers. However, a recent study by Thomas et al reported specified results concerning smoking and rectal bleeding but found no statistical significant association. With regard to inflammatory bowel disease it

is known that smoking protects the colon from inflammation. The exact mechanisms remain unclear. However, nicotine is assumed to be the active moiety and potential mechanisms may include changes in humoral and cellular immunity, changes in blood flow, colonic mucus and oxygen free radicals [22]. The same mechanisms may play a role in the case of smoking and rectal bleeding after radiotherapy.
The findings in this study concerning the co-variate age are controversial, as there seem to be a minor protective effect (OR 0.91 per unit change) of age. The findings in other studies show conflicting results, some suggesting a positive association between age and rectal bleeding [16,19], others have shown no such association [20]. When we did our analysis controlling for outliers (dropping the 2 youngest patients) the correlation disappears, thus we conclude that the primary result is not valid, and that there is no correlation between age and rectal bleeding in this study
Our series has some limitations. Scoring toxicity is complex and partly subjective to both the patient and clinician. The investigated symptom “rectal bleeding” is, though, an easy symptom to score objectively following the CTC score. The number of patients in the study is limited.

Conclusion:
The study found that CTV is a robust predictor for late rectal bleeding. None of the other investigated dosimetric or clinical parameters were significantly correlated with rectal bleeding.

Conflict of interest:
None to declare.

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Research nurse Kirsten Steffensen is acknowledged for valuable practical help.

Table 1. Patient characteristics. Range in parentheses.

Patients (n)	143	
Median age (years)	70.3 (58-80)	
Pretreatment PSA (ng/ml)	15.0 (0.6-67)	
BMI	27.4 (19-24)	
T-stage (n)		
T1	35	24.1%
T2	42	29.7%
T3	67	45.5%
T4	1	0.7%
Gleason score (n)		
6	14	9.6%
7	110	75.9%
8	11	7.6%
9	9	6.2%
10	1	0.7%
Diabetes (yes/no)	21/124	14.5%
Cardiac heart disease (yes/no)	90/55	62.1%
Other chronic disease (yes/no)	56/89	38.6%
Polyfarmacia (yes/no)	33/122	22.8%
Nicotine (yes/no)	32/113	22.1%

Polyfarmacia defined as daily use of ≥5 drugs. Nicotine = smoking during radiotherapy and at time of survey

Table 2. Summary of the results.

	Univariate analysis			Multivariate analysis		
	OR	CI(95%)	p-value	OR	CI(95%)	p-value
Cardiac heart disease	0.79	0.39-1.60	0.52			
Diabetes	1.63	0.64-4.20	0.31			
Poly-farmacia	0.70	0.30-1.66	0.42			
Anti-coagulants	0.92	0.33-2.60	0.88			
ADT	0.88	0.47-1.65	0.70			
BMI	1.02	0.93-1.12	0.66			
Age*	0.94	0.87-1.01	**0.08**	0.91	0.84-0.99	**0.03**
Smoking	0.39	0.19-1.03	**0.06**	0.41	0.14-1.19	0.10
Pre-PSA*	1.01	0.98-1.04	0.54			
T-stage	1.40	0.91-2.17	**0.13**	1.47	0.89-2.43	0.13
CTV*	1.01	1.00-1.03	**0.01**	1.01	1.00-1.03	**0.03**
Ves. sem. irradiation	1.21	0.44-3.30	0.71			
Dmax*	1.52	0.89-2.58	**0.13**	1.00	0.66-1.47	0.95
Dmean*	1.05	1.00-1.10	**0.05**	0.97	0.88-1.08	0.60
Dmin2cc*	1.18	1.01-1.39	**0.04**	1.09	0.87-1.37	0.44
V60Gy*	1.05	1.00-1.10	**0.03**	1.04	0.88-1.22	0.63
V72Gy*	1.08	1.01-1.16	**0.02**	1.01	0.85-1.22	0.85

OR= odds ratio.
Poly-farmacia ≥5 different medications.
ADT= androgen deprivation therapy.
Ves. sem. = vesicula seminalis
* Contineus variable OR per unit change

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Paper 3

Five year follow-up using a prostate stent as fiducial in image guided radiotherapy of prostate cancer.

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Acta Oncologica 2014

The aim was to evaluate five year survival and morbidity data of the first patient cohort that underwent EBRT using image-guided radiotherapy (IGRT) of localized or locally advanced prostate cancer (PC) and the removable prostate stent as fiducial.
Late genito-urinary (GU) and gastro-intestinal (GI) toxicities were scored using both the RTOG and the CTC-AE score. Urinary symptoms were also scored using the international prostate symptom score (IPSS).
Overall survival, cancer specific survival and biochemical progression free survival were 85%, 96% and 80%, respectively. Late GU and GI RTOG scores>=2 were 5% and 0%. Comparing pretreatment and post-radiotherapy IPSS indicates that development in urinary symptoms after radiotherapy may be complex.
To conclude the survival data were in accordance with recently published data. GU and GI toxicities at 5 year follow-up were low and comparable to the lowest toxicity rates reported in recent literature using modern RT like IMRT.

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ORIGINAL ARTICLE

Five-year follow-up using a prostate stent as fiducial in image-guided radiotherapy of prostate cancer

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ABSTRACT

Purpose. To report results from the five-year follow-up on a previously reported study using image-guided radiotherapy (IGRT) of localized or locally advanced prostate cancer (PC) and a removable prostate stent as fiducial.
Material and methods. Patients with local or locally advanced PC were treated using five-field 3D conformal radiotherapy (3DRT). The clinical target volumes (CTV) were treated to 78 Gy in 39 fractions using daily on-line image guidance (IG). Late genito-urinary (GU) and gastro-intestinal (GI) toxicities were scored using the radiotherapy oncology group (RTOG) score and the common toxicity score of adverse events (CTC) score. Urinary symptoms were also scored using the international prostate symptom score (IPSS).
Results. Median observation time was 5.4 year. Sixty-two of the 90 patients from the original study cohort were eligible for toxicity assessment. Overall survival, cancer-specific survival and biochemical freedom from failure were 85%, 96% and 80%, respectively at five years after radiotherapy. Late toxicity GU and GI RTOG scores ≥ 2 were 5% and 0%. Comparing pre- and post-radiotherapy IPSS scores indicate that development in urinary symptoms after radiotherapy may be complex.
Conclusions. Prostate image-guided radiotherapy using a prostate stent demonstrated survival data comparable with recently published data. GU and GI toxicities at five-year follow-up were low and comparable to the lowest toxicity rates reported. These findings support that the precision of the prostate stent technique is at least as good as other techniques. IPSS revealed a complex development in urinary symptoms after radiotherapy.

The use of fiducials in the prostate combined with image-guided radiotherapy (IGRT) has demonstrated a significant reduction in positioning uncertainties during prostate radiotherapy, and consequently the potential to reduce setup margins and irradiated volume of normal tissue [1]. Reduced setup margins may be the main explanation for the reduced radiation-induced genito-urinary (GU) and gastro-intestinal (GI) late toxicity observed in several recent studies [2–4]. The reduction in setup margins may compromise treatment efficiency as suggested in some studies [5,6]. Several other studies, however, have reported unchanged or improved biochemical freedom from failure even with reduced setup margins [2–4]. Implanted gold markers (GM) has been the standard choice as fiducial in IGRT of prostate cancer [7]. The use of a nickle titanium removable prostate stent as fiducial for co-registration of planning computer tomography (CT) and magnetic resonance imaging (MRI) and subsequent IGRT treatment has been described in detail earlier [8–12]. Advantages of the prostate stent compared to gold markers were: 1) non-invasive; 2) removable; 3) large 3D object; and 4) good signal i both CT and MR and thus well suited for MR CT co-registration of the prostate. This five-year follow-up of the clinical outcome following image-guided radiotherapy (IGRT) of localized or locally advanced prostate cancer (PC) represents a continuum of an ongoing process evaluating the removable prostate stent as fiducial.

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Material and methods

Patients

The original cohort consisted of 90 patients with local and locally advanced prostate cancer. They were treated with radical radiotherapy at the University Hospital of Aalborg Denmark from March 2007 until May 2009. The patient cohort is previously described in detail [11,12]. Exclusion from toxicity assessment was: biochemical failure, inability to read and understand the questionnaires in Danish and death. Biochemical failure was defined as an elevation of prostate-specific antigen (PSA) above nadir plus 2 ng/ml after radiotherapy. The study was in accordance with the standards of the Helsinki Declaration of 1975, as revised in 2000.

Radiotherapy

The clinical target volume (CTV) was defined as the prostate gland, or the prostate gland plus the proximal third part of the seminal vesicles in case of seminal vesicle invasion. The CTV was outlined on CT using the co-registered MRI images. An isotropic CTV to PTV margin of 5 mm was used. External beam radiotherapy (EBRT) was given using a five-field conformal plan (gantry angles at 9°, 90°, 140°, 220° and 270°). A CTV mean dose of 78 Gy in 39 daily sessions was prescribed. Constraints to organs at risk (OAR) and further treatment details are given in [11]. The Brainlab ExacTrac™ system was used for daily on-line IG positioning matching the stent with a digital reconstructed radiogram (DRR) from the planning CT. OAR dose volume histograms were exported out of the treatment planning system (TPS) and dosimetry parameters calculated in Matlab™. Patients with intermediate- and high risk according to the D'Amico classification received neo-adjuvant hormone therapy (AHT) with either LHRH analogues or non-steroidal anti-androgens for three months before irradiation, during irradiation and for a limited period thereafter, usually for one year according to the recommendations in Denmark at time of treatment.

Toxicity assessment

All eligible men were invited for a yearly clinical visit at the department of urology. The visit included a blood sample for PSA measurement and toxicity assessment using the radiation therapy oncology late radiation morbidity scoring schema (RTOG) of GU and GI toxicity. At the five-year follow-up visit this was supplemented with a telephone interview using the national cancer institute common terminology criteria for adverse events (CTC-AE) version 4.0 analogously to our previously reported three-year follow-up [12]. Urinary symptoms included frequency, urgency, incontinence, dysuria, urinary retention and hematuria. Rectal symptoms included diarrhea, fecal incontinence, proctitis, rectal pain and rectal bleeding.

Furthermore urinary toxicity was evaluated using the validated international prostate symptom score (IPSS) patient questionnaire. Patients filled in the questionnaire before prostate stent insertion, two weeks before start of the radiotherapy (baseline) and five years after end of radiotherapy.

Statistics

Survival data and biochemical freedom from failure data was calculated using the Kaplan-Meier method including all 90 patients from the original cohort. With regard to the cancer-specific survival only patients that died from prostate cancer are counted. All other patients are censored at the date of their last visit or the date of eventual non-prostate cancer-related death. Analogously, patients without biochemical failure were censored at the date of last visit or the date of death without evidence of biochemical relapse. Five year RTOG and CTC scores were tested for correlation with Gleason score, T-stage, comorbidity, seminal vesicles irradiation, smoking, use of statins and polypharmacy using contingency tables and χ^2 statistics. Five-year dichotomized RTOG and CTC scores (Grade = 0 and Grade > 0) were tested for dependency of continuous parameters, such as dosimetry parameters, age and prostate volume, using logistic regression. The dependency of RTOG and CTC toxicity scores on baseline IPSS was tested using ANOVA and t-test. Linear regression was used to test dependency of change from baseline at five year versus baseline IPSS.

Results

The median observation time was 5.4 years. Patient characteristics are shown in Table I. Of the original cohort of 90 patients, 10 patients died without biochemical failure. Three patients died of prostate cancer, and a total of 15 patients had biochemical failure. Overall survival (OS), cancer-specific survival (CSS) and biochemical freedom from failure (BFFF) with confidence interval limits are shown in Table II. The variation found concerning the high dose parameters (Dmax and V72Gy) are small (see Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.987355). This is probably due to the standardized prescribed dose and the applied OAR dose constraints in the dose planning. Patient compliance with regard to

Table I. Patient characteristics of the 60 included patients in the five year toxicity scoring.

Age (Mean (range) in years)*	68.5 (59–80)
T1	8 (13%)
T2	21 (35%)
T3	31 (52%)
Gleason score	
6	10 (17%)
7	41 (68%)
8	5 (8%)
9–10	4 (7%)
PSA (Mean (range) in ng/ml)**	15 (4–67)
Risk d'Amico classification	
Low	3 (5%)
Intermediate	14 (23%)
High	43 (72%)

*Age at study entry, ie. time of radiotherapy, **pre treatment PSA

toxicity assessment was 92% (57/62) for the RTOG score, 96% (60/62) for the CTC score and 92% (57/62) for the IPSS. A graphical representation showing peak toxicity scores are seen in Figure 1. The figure also includes our previously reported three-year toxicity CTC scores in 73 patients for completeness and comparison of the RTOG scores at three and five years. No grade 3 or higher late toxicity was registered for either RTOG or CTC at any time. RTOG toxicity grades = 2 were 5% and 0% for GU and GI, respectively. The CTC scores in Figure 1 demonstrate that the major adverse toxicities at both three and five years were urinary frequency and urgency with regard to GU toxicity (grade 2) in 13–15% of the patients and rectal bleeding with regard to GI toxicity (only grade 1) in 18% of the patients.

Significantly higher RTOG GU toxicity at five years was found related to use of statins ($p = 0.005$). Similar dependencies were observed for the CTC score at five years regarding urinary frequency ($p = 0.02$) but not for urinary urgency. The CTC scores for both urinary frequency and urgency significantly correlated to polypharmacy ($p = 0.02$ and $p = 0.03$, respectively). No significant dependencies on OAR dosimetry parameters were found for either GU or GI toxicity scores, and no correlation of OAR dosimetry parameters with statin use or polypharmacy was found.

Table II. Five-year survival data for the original stent cohort of 90 patients.

		Cum. Survival	Lo 95% CI	HR 95% CI	At risk 5 yr
OS		85%	78%	93%	77
CSS		96%	92%	100%	
BFFF	Overall	80%	72%	89%	62
	LR	100%	NA	NA	3
	IR	85%	69%	100%	16
	HR	77%	66%	88%	43

OS: Overall survival
CSS: cancer specific survival
BFFF: biochemical freedom from failure
LR: Low Risk, IR: Intermediate Risk HR: High Risk
CI: Confidence interval

IPSS data including both pretreatment and five-year follow-up results were available for 57 patients. A significant correlation between baseline IPSS and the RTOG GU score and CTC urinary frequency and urgency scores was found as shown in Table III. Table III also shows an overall statistically significant improvement in urinary symptoms at five-year follow-up compared to pretreatment based on the IPSS.

Figure 2 shows a plot of the change in IPSS at five-year follow-up from the baseline IPSS versus the baseline score. Linear regression showed a statistically significant lower IPSS change with increasing baseline IPSS after radiotherapy. Figure 2 demonstrates that the change in IPSS versus baseline IPSS was significantly lower for patients with no toxicity symptoms (RTOG score = 0) compared to patients with toxicity symptoms (RTOG score > 0), but the decrease in change was similar for the two groups.

No significant correlations were found concerning RTOG GI toxicity or CTC score for rectal bleeding.

Discussion

This paper reports the five-year follow-up results from the first clinical study using a prostate stent as fiducial during IGRT for prostate cancer. The survival data (OS: 85%, CSS 96% and BFFF 80%) are comparable with the data reported by the RTOG 9406 study (78 Gy and a 3D conformal technique) [13]. They found OS at 85%, CSS at 99% and BFFF at 80%. However, the RTOG 9406 study had a lower fraction of high risk patients compared to our study (31% vs. 71.7% in our study cohort). Comparing survival data normally requires that the risk group frequencies are similar.

Data on BFFF for high risk patients have been comprehensively reviewed using highly standardized inclusion criteria's in a recent study [14]. This review reported five-year BFFF in the range of 30–72% for high risk patients. Compared to this review our results are in the upper end of the reported range. Data from another Danish radiotherapy center has recently been reported [4]. This retrospective study compared 3D conformal with a 10 mm setup margin with IMRT combined with IGRT and a 5 mm setup margin for high risk patients. Only the three-year BFFF is reported; 86% for the 3D conformal and 90.3% for the IMRT treatment. This corresponds

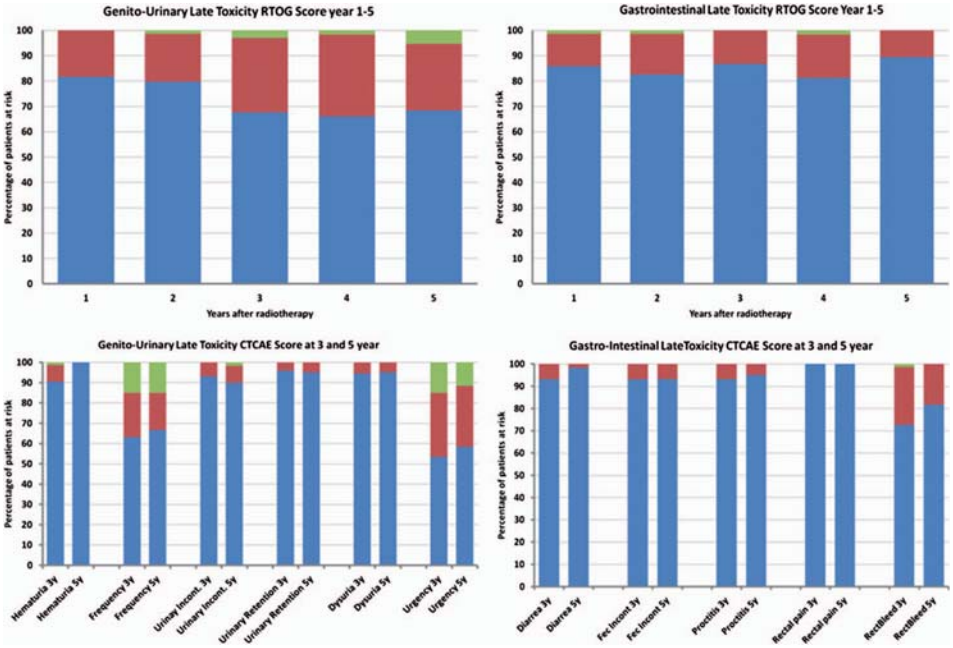

Figure 1. The upper two panels show plot of the frequencies of RTOG scored toxicities in elegible pa-tients at each year in the five year follow-up period. The genito-urinary score frequencies to the left and the gastro-intestinal score frequencies to the right. The lower two panels analogously show the corresponding CTC scores at year three and five in the folllow-up period. RTOG and CTC scores are color coded grade = 0: blue grade = 1: brown grade = 2: green.

well to the previously reported three-year BFFF of 89% for the cohort in this study [12]. Finally, a Canadian study also using a radiation dose of 79.8 Gy and IG 3D conformal treatment with a margin of 10 mm demonstrated five-year BFFF of 77.9% for high risk patients comparable to the 77% found in this study [15]. To summarize the BFFF data using the prostate stent as fiducial are comparable with other studies using similar dose and IGRT techniques. Consequently, it may be concluded that the

Table III. Baseline International prostate symptom score (IPSS) correlation with 5 year toxicity scores.

RTOG 5y*	N*	IPSS mean	IPSS StdDev	ANOVA	t-test
Grade 0	39	8.4	1.1	p = 0.0006	
Grade 1	12	12.8	1.9		
Grade 2	3	23.7	3.8		
CTC 5y urinary frequency					
Grade 0	39	8.3	1.0	p = 0.00005	
Grade 1	9	14.1	2.1		
Grade 2	9	19.0	2.1		
CTC 5y urinary urgency					
Grade 0	34	8.4	1.1	p = 0.00003	
Grade 1	16	11.5	1.6		
Grade 2	7	21.4	2.4		
All pre-treat	57	10.2	6.9		
All 5 year	57	8.5	6.7		p = 0.01

*difference in N in this group is due to non overlapping of missing RTOG scores and IPSS questionairre.

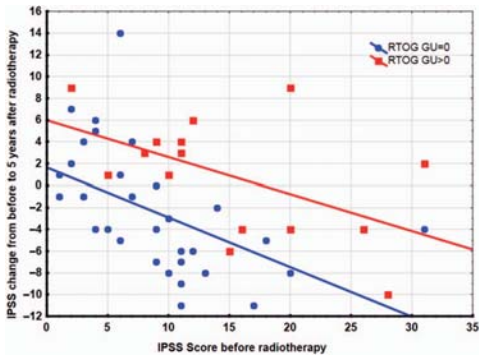

Figure 2. Changes in IPSS at five year after radiotherapy from pretreatment IPSS plotted versus pre-treatment IPSS. Linear regression lines and data points are shown for two groups: one group with RTOG toxicity score = 0 (Blue), another group with RTOG toxicity score > 0 (Red).

use of a prostate stent yields at least equal precision as gold markers.

The five-year RTOG GU and GI late toxicity grade ≥ 2 in this study were, respectively, at 5% and 0%. These frequencies are in the low end compared to the findings published in a recent review, where scores grade ≥ 2 were ranging from 5.7% to 41% and 4–33% for GU and GI toxicity, respectively [16]. The best studies applying intensity modulated radiotherapy (IMRT) in this review had a five-year mean frequency of RTOG score grade ≥ 2 of 15.5% (range 7–28.3%) and 10% (range 4–21%), respectively, for GU and GI toxicity. Data from the recently published Danish study has demonstrated a significant improvement in late toxicity at two-year observation time using IG-IMRT with a 5 mm setup margin as compared to 3D conformal radiotherapy using a 10 mm setup margin [4]. They reported RTOG grade ≥ 2 toxicity frequencies, respectively, for GU and GI for IG-IMRT of 29.7% and 5.8%, as compared to analogous frequencies of 41.8% and 57.3% for 3D conformal technique [4]. Consequently, the five-year RTOG grade ≥ 2 scores in the present study, applying a 3D conformal technique with 5 mm setup margin, were at least comparable to the toxicities for the IMRT technique reported from this other Danish center. The RTOG grade ≥ 2 toxicities in the present study are equivalent with the five-year RTOG grade ≥ 2 of 10% and 1.6% for GU and GI, respectively, reported in another recent study using IG-IMRT techniques [2]. Even though toxicity frequencies seem to lower using IG-IMRT techniques and small setup margins, these results are still controversial. Other studies have shown no effect of reducing the setup margin from 10 to 5 mm and reported similar and excellent five-year RTOG grade ≥ 2 toxicities of 6.6–7% and 1.2–2.6% for GU and GI, respectively [17]. The exclusion of patients with BF from the toxicity analysis was to avoid interference in toxicity measures from either disease recurrence or salvage therapy.

To summarize the present study has demonstrated very low GU and GI toxicity frequencies, but a caveat in the present study was a relatively small number of patients and the competing risks of death or BF, which may have led to underestimating five-year toxicity frequencies.

The RTOG and CTC scores in this study gave consistent results with regard to hematuria and rectal bleeding. Only grade = 1 toxicity was observed. An improvement in both hematuria and rectal bleeding from three to five years was observed as have been observed by others [18,19]. The complete clearance of hematuria from three to five years, however, seems unrealistic and is most probably an example of the competing risk of death. In general the CTC scores for urinary frequency and urgency were not consistent with the RTOG GU score at neither three nor five years. This inconsistency was probably due to increased frequency and urgency symptoms requiring α-blocker medications, which scores as grade 2 in CTC only.

Unexpectedly, the use of statin significantly correlated with more adverse urinary toxicities estimated on both RTOG GU scores and CTC scores at five years. The observation of increased urinary toxicity seems, most likely, to be a confounder effect, as the use of statin also correlated significantly to pre-treatment urinary toxicity estimated on IPSS and poly-pharmacy. Unfortunately, no pre-treatment scores existed for either RTOG or CTC in the present study. However, a pre-treatment (baseline) IPSS value has been recorded for most patients in the original cohort [11]. The five-year CTC and RTOG toxicity scores of urinary frequency and urge were significantly related to the baseline IPSS, again indicating that pre-treatment morbidity could have influenced the scoring at five-year follow-up. Actually, this study demonstrated that a significant overall improvement in IPSS urinary symptoms occurred at the five-year follow-up as compared to the pre-treatment IPSS level. Such an effect has been described by others [20]. Furthermore, change in IPSS at five years compared to pre-treatment levels demonstrated improvement in urinary symptoms with increasing pre-treatment IPSS as demonstrated by the regression line in Figure 2. This improvement was counteracted by manifest radiotherapy toxicity as may be seen by the upward shift of the regression line for patients with a RTOG toxicity score. Consequently, the urinary symptoms observed in this study indicate that development in urinary symptoms after radiotherapy may be more complex as counter acting effects after radiotherapy may occur over time. Such effect may complicate things when urinary late toxicity from different studies are compared. It may also explain why correlation of urinary toxicity to radiation dose may often be elusive. We recommend that future monitoring of urinary toxicity should include pre-treatment and follow-up IPSS in patients treated for localized prostate cancer with modern radiotherapy.

Conclusion

A new technique using a prostate stent as fiducial demonstrated survival data comparable with other published data. Genito-urinary and gastro-intestinal toxicities at five-year follow-up were low and comparable to lowest reported toxicities in the literature. These findings support that the precision of the prostate stent technique is at least as good as other techniques. IPSS revealed a complex development in urinary symptoms after radiotherapy.

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Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.987355.

Paper 4

MR or CT for target volume delineation in radical prostate cancer radiotherapy – five year toxicity and Quality of life outcomes

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MR target delineation reduces CTV compared to CT delineation in prostate cancer radiotherapy. The potential impact in a clinical setting on toxicity and QoL is not yet thoroughly investigated. The study compared long-term toxicity and QoL in two groups of patients using MR or CT target delineation in prostate cancer radiotherapy 5 years after therapy. The treatments were performed with the same radiation dose and PTV margins. Potential correlations with clinical and dosimetric parameters were also investigated. 120 patients were eligible for toxicity and QoL assessment. For the entire cohort overall survival 5 year overall survival was 84% and biochemical freedom from failure was 83%. The mean CTV was 18% larger in the CT group compared to the MR group. Five year toxicities were in general few and mild; no grade 3 or 4 toxicity was found. No difference in overall urinary or rectal toxicity was found despite the minor CTV volume in the MR group. No difference in global health was seen either. EORTC bowel score were significantly lower in the MR group.

The mean rectal dose and high rectal dose volumes were significantly smaller in the MR group compared to the CT group. V72 was correlated to EORTC bowel score and overall rectal toxicity.

MR or CT for target volume delineation in radical prostate cancer radiotherapy - five year toxicity and Quality of Life outcomes.

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Keywords:
Prostate neoplasm – image guided radiotherapy - MR – toxicity - QoL

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Abstract:

Background and purpose
MR target delineation reduces clinical target volume (CTV) compared to CT delineation in prostate cancer (PC) radiotherapy. Potential impact on long-term toxicity and Quality of Life (QoL) is not yet thoroughly investigated. This study compares toxicity and QoL using CT or MR delineation in PC radiotherapy.
Material and Methods
Patients were treated with high dose image guided radiotherapy (78Gy). Urinary and rectal toxicity (CTC-AE) and Quality of Life (EORTC) was assessed 5 years after radiotherapy. Potential correlations with clinical and dosimetric parameters were investigated.
Results
Of the original cohort of 202 patients 120 patients had toxicity and QoL assessed. For the entire patient cohort, five year overall survival was 84% and biochemical freedom from failure was 83%. The mean CTV was 18% larger in the CT group compared to MR. The mean rectal dose and high rectal dose volumes were significantly smaller in the MR group compared to the CT group. EORTC bowel score were significantly lower in the MR group.
Conclusions
MR delineation leads to a significantly reduced CTV and to lower rectal high dose and mean dose volumes. Late toxicities were in general few and mild in both groups. No significant differences were found. Significant less EORTC bowel symptoms were observed using MR delineation.

Introduction

External-beam radiotherapy (EBRT) is a well-established treatment in patients with prostate cancer (PC). Improved biochemical control following dose escalation up to 74-78Gy have been shown in several randomized studies, but at the cost of an increase in the treatment related late urinary and rectal toxicities (1-3). Day to day changes in patient position and variations in prostate position during the course of radiation are known sources of treatment errors. Modern radiation technology like the use of fiducials markers and image guided radiotherapy (IGRT) reduce these uncertainties and have resulted in decreased margins from clinical target volume (CTV) to planning target volume (PTV), allowing the delivery of higher radiation doses with lower frequency of late rectal and urinary toxicities (4-6). Today, the most used method is implanted gold markers (GM) combined with treatment planning on computed tomography. It is known, though, that this method leads to an overestimation of the prostate volume. Studies examining computed tomography (CT) prostate delineation compared to MR delineation has demonstrated volumes 30-40% larger following CT-delineation (7-9). Consequently the irradiated volume of normal tissue, such as urinary bladder and rectum may be smaller using MR and may improve treatment related toxicity. This could potentially, allow for further dose escalation. However, MR delineation is not

easily accessible in all radiotherapy departments, it is potentially expensive and time consuming. It is therefore of significant relevance to current practice to thoroughly evaluate long term follow-up comparing these two target delineation modalities. Consequently, the aim of the present study was to evaluate the five year toxicity and quality of life (QoL) outcomes after high dose radiotherapy in two groups of patients using either MR or CT for clinical target delineation.

Material and methods

Patients

The cohort included patients with localized or locally advanced PC (T1-T3N0M0) treated with curatively intended radiotherapy between March 2007 and May 2009 at the department of Oncology, Aalborg University Hospital. During this period, a group of 100 patients participated voluntarily in a fase 3 trail evaluating a Ni-TI stent for MR-CT co-registration and as fiducial marker. Ninety patients completed the treatment in the trail. Another consecutive group of 102 prostate cancer patients had standard planning CT and gold markers as fiducials within the chosen period. The patients were identified through searches in the patient radiation databases at the department of Oncology, Aalborg University Hospital. Reasons for exclusion from the toxicity and QoL assessment were inability to read and understand the questionnaires in Danish, death and biochemical failure (defined as nadir +2). The latter to avoid interference in toxicity measures from either disease recurrence or salvage therapy. Information on patient clinical data, co-morbidity, survival and biochemical failure was extracted from hospital patient records. The study was approved by the Regional Committee for Medical Research Ethics.

Radiotherapy treatment:

Patients were stratified into risk groups according to the d'Amico risk classification (10). Patients with intermediate or high risk received neo-adjuvant endocrine treatment with either LHRH analogues or non-steroidal anti-androgen for 3 month before irradiation. RT treatment details are described in (11). The CTV was defined as the prostate gland. In case of seminal vesicle (SV) invasion on biopsy, Partin tables > 10% risk of invasion or T3 disease, the CTV included the proximal third part of the SV. The external contours of organs at risk were outlined on the planning CT (rectum and bladder). The rectum was defined from the anal sphincter to beginning of the sigmoid. A PTV was created using an isotropic PTV to CTV margin of 5mm. Treatment planning was based on a 3D conformal technique with five conformal fields. A total of 78Gy was given in 39

fractions five days a week using the inserted fiducials for daily image guidance. The following constraints were used for normal tissue: Rectum V70<=25%, V60<=50%, dorsal part of rectum Dmax< 65 Gy and for the bladder V70<=35% and V60<=50%.

Toxicity assessment:
Toxicity and QoL was assessed for the individual patient five years after completion of his RT. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0. Urinary symptoms included haematuria, frequency, urinary incontinence, retention, dysuria and urgency. Rectal symptoms included diarrhea, fecal incontinence, proctitis, rectal pain and rectal bleeding. With regard to patient reported outcome the questionnaires used were the global life questionnaire (C30) and the prostate module (PR25) from the European Organization for Research and Treatment of Cancer (EORTC). Chosen outcome measures from the C30 questionnaire were the different functional scales, the global health score and the symptom scales "pain" and "fatigue". From the PR25 the chosen outcome scales were the Urinary symptoms (eight items), bowel symptoms (four items) and sexual activity (two items).

Statistics:
Overall survival (OS) and biochemical freedom from failure (BFFF) were calculated using the Kaplan-Meier method. Patient characteristic and late toxicity score comparisons were made between the CT and MR groups, using the t-test or Mann-Whitney test for continuous variables and χ^2 or Fisher's exact test for categorical variables. The CT group was used as a reference when comparing the two treatment groups. Scores for patient-reported outcomes in terms of the EORTC QoL questionnaires were analysed according to the EORTC scoring manual (12;13). For ease of statistical interpretation, all scale and item scores were linearly transformed to a scale from 0 to 100. For the functional functional scales and the global quality-of-life scale, a high score represents a good level of functioning. For the symptom scales and items, a high score corresponds to more severe symptoms. Missing data was handled as recommended by the EORTC. Possible correlations between the different outcomes were tested by univariate (UVA) and eventually multivariate (MVA) linear or logistic regression models. The toxicity data were transformed into binary values either grade 0 or ≥1 before doing eventual logistic regression analysis. P-values are two-sided and statistical significance was set at 5%. The data were analysed using STATA v11 (Stata statistical software version 11; Stata Corporation).

Results

Patient flow is shown in Figure 1. Thirteen of the 202 patients came from other regions or countries and had no follow-up at all in the department. Characteristics of the remaining 189 patients are shown in table I. The two groups were comparable with respect to the clinical risk factors: Gleason score, pre-treatment PSA, inclusion of SV in the CTV, age, smoking and haemorrhoids. Significantly higher T-stages and risk group classifications were present in the MR group compared to the CT group. There was no difference observed between the two groups considering co-morbidity: diabetes, cardio-vascular disease, chronic obstructive pulmonary disease (COPD), and other chronic diseases (data not shown), neither in the use of medications.

The size of the groups and number of events were too small to give statistical power to compare survival data between the two groups. For the total cohort overall survival was 0.84 and the biochemical failure free survival data was 0.83 with a median observation after RT of 5.4 years. The mean CTV volumes were 42 cm^3 versus 50 cm^3 for the MR and CT group, respectively, and thus 18% larger in the CT group compared to the MR group.

120 patients were eligible for the toxicity and QoL scoring. One of these patients accepted toxicity assessment but did not fill out QoL questionnaires because of end stage ENT cancer. Another patient filled out the PR25 but chose not to fill out the C30 because of severe COPD and daily oxygen requirement.

In general, the late side effects were few and mild in both groups. No grade 3 or 4 toxicity was registered. The 5 year rectal and urinary toxicity scores are shown in table II. No difference in overall rectal or urinary toxicity (table III) between the groups were found (p=0.84 and p=0.16, respectively). Overall rectal toxicity was correlated to v72 (p=0.02) and logCTV (p=0.03) doing a UVA logistic regression analysis. Concerning the rectal symptoms the most frequent finding was rectal bleeding grade 1 in both groups. Rectal bleeding was correlated to logCVT (p=0.01), v72Gy (p= 0.01) and inclusion of SV in the CTV (p=0.02) in a UVA logistic regression analysis. No significant difference was found in the incidence of the different rectal symptoms between the groups, though diarrhoea showed a tendency of being less frequent in the MR group with borderline significance (p=0.06). There was no influence of age, T-stage, Gleason score, pre-treatment PSA, CTV, seminal vesicles irradiation or the dosimetric parameters on the development of the rectal symptoms except as mentioned above.

Regarding urinary toxicity patients in both groups were mainly bothered with increased urinary frequency and urgency grade 1 and 2. Toxicities were similar in the two groups, though with borderline significance concerning haematuria and urinary frequency, both showing the trend to be less frequent in the MR group (p=0.06 for both). There was no influence of age, T-stage, Gleason score, pretreatment PSA, CTV, or any of the dosimetric data on the development of urinary toxicity.

EORTC QoL results are presented in table IV. In general, they showed a high level of functioning and a low level of symptoms in both groups. The bowel symptom score differed significantly between the 2 groups (p=0.01) being lower in the MR group. The cognitive score was also significantly different otherwise the groups had similar QoL outcomes. No correlation was found between the QoL scores and age.

The EORTC urinary score correlated significantly with the overall urinary toxicity score likewise the QoL bowel score was significantly correlated with the overall rectal toxicity score (p=0.001 for both).

Table V show the dose characteristics for the OAR: rectum and bladder. No difference in rectal or bladder volume was observed between the two groups. But rectal mean dose and high dose volumes (v50gy, v60gy and v72gy) were significantly lower in the MR group compared to the CT group, in accordance with the observed difference in CTV. Analogously, lower mean and high dose volumes were observed for the bladder in the MR group, although not statistically significant.

Discussion

This study aimed at comparing toxicity and Quality of Life outcomes after radical radiotherapy for localized or locally advanced prostate cancer in two groups using MR or CT imaging for CTV delineation. The average CTV was 18% larger in the group with CT delineation compared to MR delineation. Possible explanations of the difference in the present study could be that the distribution of the true prostate volumes was different between the MR and CT group. Different papers have demonstrated that there is an association between high grade cancers and a smaller prostate volume (14;15). This could be a possible confounder in that the MR group had a significantly higher number of high risk patients. The d'Amico risk group classification consists of the three outcomes: Gleason score, PSA level and T-stage. In this study, there was no significant difference in the matter of the Gleason-score, thus the potential confounder can probably be neglected in this case. Neoadjuvant hormonal treatment is also known to reduce prostate size,

however the distribution between the groups were equal in the present study (p=0.41). The 18% difference between CT and MR delineation was considerably less than previously reported difference of 30-40% (7-9;16). A possible explication of the reduced CTV difference compared to other studies could be that the regular use of MR in our centre may have impacted the physicians experience in outlining the prostate on CT (8), and thus reduced the difference between the CT and MR group. The similar toxicities between the two groups found in the study may also be a result of this.

The size of the groups and number of events were too small to give statistical power to compare survival data between the two groups. But the OS and BFFS for the total patient population in the present study were comparable to newly published results regarding high dose 3D conformal EBRT (17;18).

Late urinary and rectal toxicity 5 years after radiotherapy were mainly grade 0 or 1 in the present study. Maximum toxicity score was grade 2, which was observed in 10% and <1% of the patients concerning the urinary and rectal toxicity, respectively. The values are low compared to the results published in a recent review (19). In this review the 5 year late toxicity grade>=2 was ranging from 6-41% and 4-33% concerning urinary and rectal toxicity, respectively. The lowest toxicity rates found in the review were in studies applying IMRT. These studies had a mean frequency of grade>=2 toxicity of 15.5% (range 7-28.3%) regarding the urinary toxicity and 10% (range 4-21%) regarding the rectal toxicity.

In the present study, no significant difference in 5 year late urinary toxicity was found between the MR and CT groups. Haematuria and frequency showed the tendency to be more pronounced in the CT group (both p=0.06). This could be an effect from the use of MR for prostate delineation, as the bladder wall may be excluded from the CTV on MR, this is not possible using CT. No difference between the groups relating to the dosimetric data to the bladder was found. There was a trend towards a smaller bladder high dose volume in the MR group compared to the CT group, however not statistically significant. With the relatively small number of patients in mind, the observed tendency could be due to the competing risk of death before 5 years.

With regard to the rectal toxicity no significant differences between the two groups were found. A trend towards less diarrhoea was observed in the MR group compared to the CT group (p=0.06). The rectal high dose volume (v72gy) was found to be significantly smaller in the MR group compared to the CT group. Both logCTV and v72gy were correlated with rectal bleeding and overall rectal toxicity. But no significant difference in rectal toxicity was observed between the

groups. The missing difference in rectal bleeding may be explained by the fact that the difference in CTV between the MR and CT group was small, and the average v72gy values were low in both groups, in accordance with the observed low frequency of rectal bleeding. Finally the low toxicity frequencies combined with the limited number of patients in the study may have limited the detection of significant differences.

The QoL assessment showed no significant differences between the two groups except for cognitive functioning and bowel symptoms, where the MR group had higher cognitive functioning and lower bowel symptom score. Age and co-morbidities, that could otherwise influence QoL, did not differ between the groups. OoL can be affected both by the disease as well as the treatment. The risk of disease recurrence was higher in the MR group because of the significantly higher number of high risk patients. This could possibly influence QoL, but without baseline scores from both groups no reliable analysis could be done.

The EORTC bowel symptom score was significantly smaller in the MR group compared to the CT group, though only defined as a minor difference according to Osoba (20) and may not be clinically relevant. This observed difference could be due to pre-treatment differences between the two groups. However, the EORTC bowel symptom score was highly correlated to overall rectal toxicity. The findings of a reduced logCTV and v72 in the MR group and their correlation with overall rectal toxicity suggest that a difference in late radiation toxicity is a likely explanation for the lower bowel symptom score observed in the MR group compared to the CT group.

The difference found relating to cognitive functioning is not interpreted as a result of the different treatment setups, but may be a selection bias in that patients with high cognitive functioning may be more likely to accept participation in medical trails. This can explain the higher cognitive functioning in the MR group.

Urinary toxicities seem to be the most frequent cause of treatment related symptoms in the era of modern radiotherapy and should be part of future work. No significant data was found in this study, that MR delineation compared to CT delineation reduces urinary toxicity. Urethra sparing has so far been considered controversial because of concerns for under dosage of the peri-urethral tissue. A recent theoretical study using MR delineation and the Ni-TI stent as fiducial, combined with IMRT demonstrated that lower urinary toxicities may be possible without compromising tumour control (21).

A delicate balance exists aiming for both maximum accuracy (high BFFS) and maximum margin reduction (low toxicity). The extent of microscopic disease remains uncertain because of limits in

imaging modalities. Recent reports of decrease in BFFS have been published (22-24). The potential benefit of an inaccurate CTV could be that it accounts for errors that we would normally consider part of the PTV expansion. The development in modern imaging technology will hopefully help solving this problem.

Limitations in this study are as mentioned before a small number of both patients and events, this limits the statistical power. Baseline assessments before RT would be preferable to better evaluate both toxicity and QoL. This may be particularly relevant in an elderly patient population like prostate cancer patients as some symptoms may be due to undetected co-morbidity progression. The utilisation of MR in patient work-up process is potentially expensive, time consuming and not always accessible in all radiotherapy departments. It may be discussed whether the differences in bladder and rectal toxicity between the MR and CT group observed in this study are clinically relevant. The effect of MR delineation will require further confirmation with future prospective studies on more patients and longer follow-up to evaluate the clinical relevance in term of possible toxicity reduction and gain in QoL.

Conclusions

The clinical target volume and the rectal high dose volume (v72Gy) were significantly smaller in the MR group compared to the CT group. Significantly less EORTC bowel symptoms was observed in the MR group compared to the CT group. No difference in urinary toxicities was observed between the MR and CT group.

Conflict of interest

None to declare.

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CHAPTER 8. DISCUSSION

The following discussion will relate to the most central aspects of this PhD thesis evaluating a new treatment modality using MRI target planning and a Ni-Ti prostate stent as fiducial marker for both MR-CT co-registration and IGRT. The background for the projects was the search of better target planning before therapy and better visualization during therapy; ultimately to try to optimize treatment results but minimize treatment related side-effects. More specific discussions of the findings of the studies can be found in the discussion sections of the corresponding papers I-IV.

Toxicity following curative treatments of any cancer is a crucial issue and toxicity reduction is a general ambition irrespective of the treatment modality. With regard to PCa patients the issue becomes extremely relevant since the group of patients that are offered the curative treatments, most often have no symptoms of their cancer disease at all. The number needed to treat is high with regard to prostate cancer. In the case of PSA screening, one reference study reported that 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer (123). Furthermore, the indolent nature of the disease affecting mostly elderly men comes to that many of the PCa patients will die of other causes but with the potential side-effects following the curative treatment.

The theoretical advantage of MRI delineation would be a reduced and a more accurate CTV. We found a significant difference in CTV between the group with CT delineation compared to MRI delineation with 18% larger volumes in the CT group (5 year results). Possible explanations of the difference could be that the distribution of the true prostate volumes was different between the MR and CT group. Different papers have demonstrated that there is an association between high grade cancers and a smaller prostate volume (124;125). This could be a possible confounder in that the MR group had a significantly higher number of high risk patients. The d'Amico risk group classification consists of the three outcomes: Gleason score, PSA level and T-stage. In this study, there was no significant difference in the matter of the Gleason-score, thus the potential confounder can probably be neglected in this case. Neoadjuvant hormonal treatment is also known to reduce prostate size, however the distribution between the MR and CT groups were equal ($p=0.41$).

The 18% volume difference between CT and MRI delineation was considerably less than previously reported difference of 30-40% (53-56). The contouring variation seen using MRI is lower than with CT because of the superior distinction of the prostate from adjacent structures on MRI.

However, with training, these structures can many times be recognized on CT scans as well (55). The regular use of MRI in our centre may have impacted the physicians experience in outlining the prostate on CT, and thus reduced the difference between the two groups. However, the results still showed that a significant reduction in CTV after MRI delineation compared to CT delineation is feasible in clinical practice.

The 5 year follow-up using the RT technique based on the Ni Ti stent demonstrated in paper III that survival rates (OS: 85%, BFFS: 80%) were comparable with the recent RTOG study 9406 (86) where OS: 85% and BFFS: 80% were found in the matter of 3D-CRT (78Gy) treatment. Even if the RTOG 9406 study had a lower fraction of high risk patients compared to our study cohort (31% vs. 72%). The 5 year RTOG toxicity scores 2≥ were very low (GU toxicity 5% and GI toxicity 0%). A recent review published toxicity scores ≥2 ranging from 5.7-41% and 4-33% for GU and GI toxicity, respectively (126). A study using IMRT techniques have reported 5 year RTOG ≥2 scores of 10 and 1.6% for GU and GI, respectively (91). We conclude that the RT technique based on the Ni-Ti stent as marker during IGRT for PCa yields a precision at least as good as other techniques.

The size of the two groups and number of events were too small to give statistical power to compare survival data between the two groups. But 5 year OS and BFFS for the total patient population were comparable to newly published results regarding high dose 3D conformal EBRT (86;127).

The results of the 3 and 5 year toxicity assessments after either MRI or CT delineation in paper I and IV showed in both assessments very low CTC-AE toxicity rates. As mentioned, the regular use of MRI in our centre may have impacted the physicians experience in outlining the prostate on CT. This may have influenced the quite similar toxicities. No difference in overall rectal or urinary toxicity was found at 3 or 5 years. At 3 years follow-up less urinary frequency and urinary retention was found in the MR group, at 5 years this significant difference had disappeared but less diarrhoea was then found in the MR group. The CTV was at 3 years found correlated to both rectal bleeding and overall rectal toxicity, at 5 years the correlation with overall rectal toxicity disappeared but a correlation between rectal bleeding and both CVT and v72Gy was found. The toxicity levels were at both assessments comparable with data from the literature (91;126;128).

Urinary toxicities seem to be the most frequent cause of treatment related symptoms in the era of modern radiotherapy as confirmed in paper I and IV. No significant data was found in these studies, that MR delineation compared to CT delineation reduces urinary toxicity in long-term follow-up. Urethra sparing has so far been considered controversial because of concerns for under dosage of the peri-urethral tissue. A recent theoretical study using MRI delineation and the Ni-TI stent as fiducial, combined with

IMRT demonstrated that lower urinary toxicities may be possible without compromising tumour control (129).

The QoL assessment at 5 year follow-up showed no significant differences between the two groups except for cognitive functioning and bowel symptoms. The MR group had higher cognitive functioning and lower bowel symptom score. Age and co-morbidities, that could otherwise influence QoL, did not differ between the groups. OoL can be affected both by the disease as well as the treatment. The risk of disease recurrence was higher in the MR group because of the significantly higher number of high risk patients. This could possibly influence QoL, but without baseline scores from both groups no reliable analysis could be done.

The EORTC bowel symptom score was significantly smaller in the MR group compared to the CT group, though only defined as a minor difference according to Osoba (130) and may not be clinically relevant. In our study the difference in EORTC bowel symptom score correlated well with the observed lower frequency of diarrhoea in the MR group. These observations could be due to pre-treatment differences between the two groups. However the EORTC bowel symptom score was also correlated to overall rectal toxicity and furthermore to the rectal high dose volume (v72gy). These findings suggest that a difference in late radiation toxicity is a likely explanation for the lower bowel symptom score observed in the MR group compared to the CT group. The difference found relating to cognitive functioning is not interpreted as a result of the different treatment setups, but may be a selection bias in that patients with high cognitive functioning may be more likely to accept participation in medical trails. This can explain the higher cognitive functioning in the MR group.

No difference between the groups relating to the dosimetric data to the bladder was found. There was a trend towards a smaller bladder high dose volume in the MR group, however not statistically significant.

The dosimetic data to the rectum differed between the two groups in the matter of high dose (v50, v60 and v72Gy) as well as rectal mean dose. All of them significantly lower in the MR group. The logCTV and v72gy were correlated with rectal bleeding at 5 years ($p=0.05$ and $p=0.01$, respectively). But no significant difference in rectal bleeding toxicity score or any of the other chosen rectal symptoms was observed (except diarrhoea as mentioned). The missing difference in rectal toxicity may be explained by the fact that the difference in CTV between the MR and CT group was small, and the average v72gy values were low in both groups, in accordance with the observed low frequency of rectal bleeding. A larger patient population would probably be required to demonstrate a difference in rectal toxicity between the groups. The strong correlation found in paper II between CTV and rectal bleeding and the finding of a smaller CTV in the

MR group in this study sustain this theory. The prostate cancer dose escalation trial, RTOG 9406 also found that larger PTVs were associated with increased rectal toxicity (131). Several other studies have evaluated rectal dose-volume histograms and have found consistent results on the dose-volume effect on the probability of developing rectal bleeding (132-135). Both the absolute and the percentage of rectal volume receiving the highest doses (>60Gy) are correlated with rectal bleeding (111). As the CTV increases a larger volume of the rectum is at risk of high dose irradiation thus explaining the increased risk of rectal bleeding.

Otherwise established risk factors for late rectal toxicity include advanced age (114), larger rectal volume (136), diabetes mellitus (113;114;137;138), prior abdominal surgery (138), use of androgen deprivation (139;140), haemorrhoids (111;141) or inflammatory bowel disease (142). Furthermore acute rectal toxicity is associated with an increased risk of late rectal toxicity (143;144). The latter raises the interesting question to whether early intervention to lessen acute toxicity might also reduce the risk of late toxicity.

Limitations in these studies are as mentioned before a small number of both patients and events, this limits the statistical power. The very low toxicity rates found combined with the relatively small number of patients in the studies and the non-negligible competing risks of death and biochemical failure, may have led to an underestimation of the toxicity frequencies found. Baseline assessments before RT would be preferable to better evaluate both toxicity and QoL. This may be particularly relevant in an elderly patient population like prostate cancer patients as some symptoms may be due to undetected co-morbidity progression. Age-matched control groups are known to be affected by significant urinary problems (145).

A delicate balance exists aiming for both maximum accuracy (high BFFS) and maximum margin reduction (low toxicity). The exact incidence and extent of microscopic disease remains uncertain because of limits in imaging modalities. A study from Heemsbergen et al. (146) has reported fewer clinical failures for high-risk prostate cancer patients treated with rectangular fields, compared to conformal fields underlining the above mentioned problem. Recent reports of decrease in BFFS after margin reduction have also been published (69;73;147). A relevant question is raised: Maybe margins can be too tight, thus compromising clinical failure and in the end survival. The extent of microscopic disease remains uncertain because of limits in imaging modalities (147). The potential benefit of an inaccurate CTV could be that it accounts for errors that we would normally consider part of the PTV expansion. Future developments in modern imaging technology will hopefully help solving this problem.

MRI delineation and MR-CT co-registration is today feasible as part of IGRT treatment for prostate cancer. The utilisation of MRI in patient work-up process is potentially expensive, time consuming and not always accessible in all radiotherapy departments. It may be discussed whether the differences in toxicity and QoL between the MR and CT group observed in these studies are clinically relevant. The effect of MRI delineation will require further confirmation with future prospective studies on more patients and longer follow-up time to evaluate the clinical relevance in term of possible toxicity reduction and gain in QoL.

CHAPTER 9. CONCLUSIONS

Four papers are included in this ph.d thesis. The main conclusions are summarized below.

• MRI delineation and MR-CT co-registration is feasible as part of IGRT treatment for prostate cancer.

• MR delineation is followed by a significant reduction in CVT compared to CT delineation – also in a clinical setting.

• Significantly lower rectal high doses and mean doses were found after MR delineation.

• CTV was found to be the most consistent risk factor for rectal bleeding after PCa RT

• Toxicity levels after modern RT of prostate cancer are very low both using standard CT delineation and MRI delineation

• Urinary toxicities are the most frequent toxicities after prostate RT.

• No difference in overall rectal or urinary toxicity after 3 or 5 years was found after MRI or CT delineation

• No difference in EORTC global health score was registered after MRI or CT delineation.

• Significantly lower EORTC bowel score was found in the MR group.

• The EORTC bowel score was correlated to CTC-AE overall rectal toxicity and v72Gy.

Ongoing studies:

Baseline assessment of QoL in a cohort of Danish men undergoing radical RT.

Acute toxicity in men undergoing high dose IGRT for PCa after MRI target planning and with the use of a prostate stent as fiducial marker.

Prospective toxicity follow-up at baseline, 1, 3 and 5 years after radiotherapy using MRI target delineation and IGRT.

Prospective changes in QoL during modern high dose RT.

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APPENDICES

Appendix A. EORTC questionnaires

EORTC QLQ-C30 (version 3.0)

Vi er interesserede i at vide noget om dig og dit helbred. Vær venlig at besvare alle spørgsmålene selv ved at sætte en ring omkring det svar (tal), som passer bedst på dig. Der er ingen "rigtige" eller "forkerte" svar. De oplysninger, som du giver os, vil forblive strengt fortrolige.

Skriv venligst dine forbogstaver her: |_|_|_|_|
Din fødselsdato (dag, måned, år): |_|_|_|_|_|_|_|_|
Dato for udfyldelse af dette skema (dag, måned, år): 31 |_|_|_|_|_|_|_|_|

	Slet ikke	Lidt	En del	Meget
1. Har du nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert?	1	2	3	4
2. Har du nogen vanskeligheder ved at gå en lang tur?	1	2	3	4
3. Har du nogen vanskeligheder ved at gå en kort tur udendørs?	1	2	3	4
4. Er du nødt til at ligge i sengen eller at sidde i en stol om dagen?	1	2	3	4
5. Har du brug for hjælp til at spise, tage tøj på, vaske dig eller gå på toilettet?	1	2	3	4

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
6. Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?	1	2	3	4
7. Var du begrænset i at dyrke dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8. Havde du åndenød?	1	2	3	4
9. Har du haft smerter?	1	2	3	4
10. Havde du brug for at hvile dig?	1	2	3	4
11. Har du haft besvær med at sove?	1	2	3	4
12. Har du følt dig svag?	1	2	3	4
13. Har du savnet appetit?	1	2	3	4
14. Har du haft kvalme?	1	2	3	4
15. Har du kastet op?	1	2	3	4

Vær venlig at fortsætte på næste side

I den forløbne uge:	Slet ikke	Lidt	En del	Meget
16. Har du haft forstoppelse?	1	2	3	4
17. Har du haft diarré (tynd mave)?	1	2	3	4
18. Var du træt?	1	2	3	4
19. Vanskeliggjorde smerter dine daglige gøremål?	1	2	3	4
20. Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?	1	2	3	4
21. Følte du dig anspændt?	1	2	3	4
22. Var du bekymret?	1	2	3	4
23. Følte du dig irritabel?	1	2	3	4
24. Følte du dig deprimeret?	1	2	3	4
25. Har du haft svært ved at huske?	1	2	3	4
26. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort dit familieliv?	1	2	3	4
27. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort din omgang med andre mennesker?	1	2	3	4
28. Har din fysiske tilstand eller medicinsk behandling medført økonomiske vanskeligheder for dig?	1	2	3	4

Ved de næste 2 spørgsmål bedes du sætte en ring omkring det tal mellem 1 og 7, som passer bedst på dig

29. Hvordan vil du vurdere dit samlede helbred i den forløbne uge?

1	2	3	4	5	6	7
Meget dårligt						Særdeles godt

30. Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?

1	2	3	4	5	6	7
Meget dårlig						Særdeles god

EORTC QLQ - PR25

Patienter fortæller undertiden, at de har følgende symptomer eller problemer. Anfør venligst, i hvilket omfang du har haft disse symptomer eller problemer inden for den forløbne uge. Besvar spørgsmålene ved at sætte en ring omkring det tal, som passer bedst til dig.

I den forløbne uge:	Slet ikke	Lidt	En del	Meget
31. Har du ofte skullet lade vandet i **løbet af dagen**?	1	2	3	4
32. Har du ofte skullet lade vandet i **løbet af natten**?	1	2	3	4
33. Når du har følt trang til at lade vandet, har du skullet skynde dig på toilettet?	1	2	3	4
34. Har du haft svært ved at få nok søvn, fordi du ofte skulle lade vandet om natten?	1	2	3	4
35. Har du haft problemer med at forlade hjemmet, fordi du var nødt til at være i nærheden af et toilet?	1	2	3	4
36. Har du haft ufrivillig vandladning (udløb)?	1	2	3	4
37. Har du haft smerter under vandladningen?	1	2	3	4
38. Dette spørgsmål skal kun besvares, hvis du benytter en inkontinens hjælpeanordning. Har det været et problem for dig at anvende en inkontinens hjælpeanordning?	1	2	3	4
39. Har dine daglige aktiviteter været hæmmet af dine vandladningsproblemer?	1	2	3	4
40. Har dine daglige aktiviteter været hæmmet af dine afføringsproblemer?	1	2	3	4
41. Har du oplevet ufrivillig afføringsudtømning (udløb)?	1	2	3	4
42. Har du haft blod i afføringen?	1	2	3	4
43. Har du haft en oppustet fornemmelse i maven?	1	2	3	4
44. Har du haft hedeture?	1	2	3	4
45. Har du haft ømme eller hævede brystvorter eller bryster?	1	2	3	4
46. Har du haft hævelser i ben eller ankler?	1	2	3	4

fortsættes på næste side

I de sidste fire uger:	Slet ikke	Lidt	En del	Meget
47. Har du haft problemer med vægttab?	1	2	3	4
48. Har du haft problemer med vægtforøgelse?	1	2	3	4
49. Har du følt dig mindre maskulin som følge af din sygdom eller behandling?	1	2	3	4
50. I hvor høj grad har du haft lyst til sex?	1	2	3	4
51. I hvor høj grad har du været seksuelt aktiv (med eller uden samleje)?	1	2	3	4

FØLGENDE FIRE SPØRGSMÅL SKAL KUN BESVARES, HVIS DU HAR VÆRET SEKSUELT AKTIV I DE FORLØBNE 4 UGER

52. I hvor høj grad har du nydt at dyrke sex?	1	2	3	4
53. Har du haft problemer med at få eller bevare en erektion?	1	2	3	4
54. Har du haft sædudtømmelsesproblemer (f.eks. tør sædudtømmelse)?	1	2	3	4
55. Har du følt ubehag ved at være seksuelt intim?	1	2	3	4

Appendix B. IPSS questionnaire

Spørgsmål vedrørende din vandladning. Udfyld venligst skemaet ved at sætte ring om tallet ved det udsagn, som bedst besvarer spørgsmålet.

	Aldrig	Mindre end 1 ud af 5 gange	Mindre end halvdelen af gangene	Ca. halvdelen af gangene	Mere end halvdelen af gangene	Næsten altid	
1. Hvor mange gange har du gennem den sidste måned, haft fornemmelsen af, at blæren ikke blev tømt ordentligt efter endt vandladning?	0	1	2	3	4	5	
2. Hvor mange gange har du gennem den sidste måned, måttet lade vandet med mindre end 2 timers mellemrum?	0	1	2	3	4	5	
3. Hvor mange gange har du gennem den sidste måned oplevet, at vandladningen foregår afbrudt over flere omgange?	0	1	2	3	4	5	
4. Hvor mange gange har du gennem den sidste måned følt en bydende stærk vandladnings trang som gjorde, at De straks måtte lade vandet?	0	1	2	3	4	5	
5. Hvor mange gange har du gennem den sidste måned oplevet en svag strålekraft?	0	1	2	3	4	5	
6. Hvor mange gange har du gennem den sidste måned måttet presse for at vandladningen kunne komme igang?	0	1	2	3	4	5	
	Ingen	1 gang	2 gange	3 gange	4 gange	5 gange eller flere	
7. Hvor mange gange har du gennem den sidste måned gennemsnitlig måttet stå op om natten for at lade vandet?	0	1	2	3	4	5	
						Total IPSS score	
Livskvalitet passende til urinvejssymptomer							
	Henrykt	Tilfreds	Over-vejende tilfreds	Blandet tilfreds/ utilfreds	Overvejende utilfreds	Ulykkelig	Desperat
1. Hvis du skulle leve resten af livet med din vandladning som den foregår nu, ville du så være	0	1	2	3	4	5	6

SUMMARY

A significant increase in the prostate cancer incidence has made prostate cancer a major health problem in recent years. Because of the often but unfortunately not always indolent nature of the disease, over-diagnosis and over-treatment are relevant clinical and ethic dilemmas.

External beam radiotherapy is a well established treatment modality for prostate cancer. Accuracy and precision are key words with regard to optimal survival and minimal toxicity in modern radiotherapy and are fundamentals in modern radiotherapy.

Modern imaging has improved the ability to define radiotherapy target volumes. Especially treatment margins have been reduced through the use of more accurate treatment planning and image-guided technology.

Increasing doses have lead to increased disease control. Aiming for minimal toxicity after radiotherapy, magnetic resonance imaging delineation could be a possible tool, knowing that clinical target volumes are up to 30% smaller on MRI delineation compared to computer tomography delineation.

The overall aim of the thesis was to explore the use of MRI target planning and a Nicle-Titanium prostate stent as fiducial marker for both MR-CT co-registration and image guided radiotherapy.

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